driving force in forming the dimer over any possible disproportionation products. Further work is in progress in the direction of the synthesis of 1-lithio-2,2-di-*tert*-butylethene and its thermal rearrangements.

It is very interesting to note that two completely different synthetic routes lead to the same dilithiotrimethylenemethane compound. This ionic form therefore definitely represents an energy minimum. This finding would add support for the thesis of Streitwieser and coworkers that many polylithium organic compounds are of a highly ionic nature.[15]

Acknowledgment. We are grateful to the National Science Foundation (CHE-8521390) and the Robert A. Welch Foundation (F-700) for support of this work.

(15) (a) Streitwieser, A. J.; Williams, J. E.; Alexandratos, S.; McKelvey, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 4778. (b) Collins, J. B.; Streitwieser, A. J. *J. Comput. Chem.* **1980**, *1*, 81.

Radical Cyclization Strategies to Bridged Systems. Synthesis of Bicyclo[3.2.1]octan-3-ones from (*S*)-Carvone[1]

A. Srikrishna* and P. Hemamalini

Department of Organic Chemistry, Indian Institute of Science, Bangalore - 560 012, India

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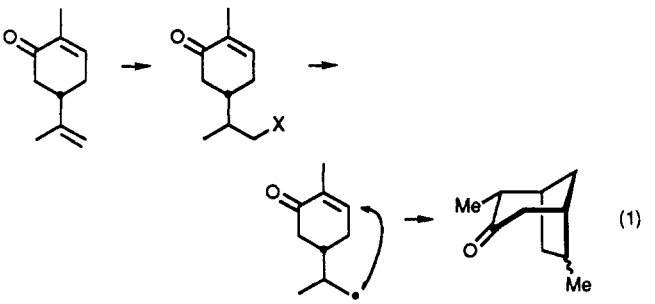
Radical cyclization of the bromo enones **2a–e**, obtained by regiospecific bromoetherification reaction on the electron-rich double bond of (*S*)-carvone (**1**), furnished regio- and stereospecifically bicyclo[3.2.1]octan-3-ones **3a–e** and **4a–e**. Analogously, radical cyclizations of the alcohols **6** and **7** gave bicyclo[3.2.1]octan-3-ols **8** and **9**, and the bromo enones **11a,b** gave the bridgehead-substituted bicyclo[3.2.1]octan-3-ones **12a,b** and **13a,b**.

The development of synthetic methods for the preparation of bridged systems has been stimulated by the discovery of polycyclic natural products that incorporate bridged systems as part structures. The bicyclo[3.2.1]octane system has received a relatively large amount of attention[2] due to its frequent presence in various sesqui- and diterpenoids. In the last decade there has been an upsurge of interest in the application of free-radical cyclization for the synthesis of fused carbo- and heterocyclic systems.[3] Even though the first report of formation of a bridged system by a radical cyclization reaction appeared in 1983, until recently, relatively little attention was given to the synthesis of bridged[4] systems by transannular radical cyclizations.[5]

In our quest for a simple method for the construction of chiral bicyclo[3.2.1]octanes, we conceived of a two-step sequence (eq 1) wherein carvone (**1**) is converted into a radical precursor, by manipulation of the electron-rich olefin, and regiospecific intramolecular addition of the radical to the enone moiety. This sequence has several attractive features, including the commercial availability of both the enantiomers of carvone (**1**), formation of two new stereocenters in a regio- and stereospecific way, and flexibility to provide more functionalized bicyclo[3.2.1]-



(1)

octanes. In this account, we report a general, efficient, and preparative route to chiral bicyclo[3.2.1]octan-3-ones and describe its extension to the bridgehead-substituted systems present in variety of natural products.

The sequence is depicted in the Scheme I. The radical derived from the bromide **2**, obtained from carvone by a bromoetherification reaction, on 5-*exo-trig* cyclization followed by abstraction of hydrogen from tin hydride furnishes the bicyclic systems. Thus, *N*-bromosuccinimide (NBS) bromination of the electron-rich olefin in (*S*)-carvone (**1**) in methanol–methylene chloride medium furnished an inseparable mixture (1:1 by ^{13}C NMR) of 4*S*,8*R* and 4*S*,8*S* diastereomeric methoxy bromides **2a** in a regiospecific manner. Refluxing a 0.02 M benzene solution of the bromide mixture **2a** with 1.1 equiv of tri-*n*-butyltin hydride (TBTH) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) for 3 h cleanly furnished, in 82% yield, a separable mixture of endo and exo bicyclic products **3a** and **4a**. The structures were delineated through their spectral data. Both **3a** and **4a** have bands at 1700 cm^{-1} (saturated carbonyl group) in their IR spectra and saturated carbonyl carbon resonances in their ^{13}C NMR spectra (δ 211.4 and 212.5). The absence of olefinic carbons in the ^{13}C NMR spectra, and olefinic proton, olefinic methyl, and bromomethylene resonances in the ^1H NMR spectra further support the cyclic structures. The presence of methyl doublets at δ 1.03 and 0.99 in the ^1H NMR spectra clearly establish not only the cyclization but

(1) Part 4 in the series: Chiral synthons from carvone. Part 3: Srikrishna, A.; Hemamalini, P. *Indian J. Chem.* **1990**, *29B*, 201.

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(4) Some aspects of difficulty in bridge formations by the tin hydride method are discussed in ref 3b, sec. 5.2.2.

(5) For earlier reports, see: Stork, G.; Baine, N. H. *Tetrahedron Lett.* **1985**, *26*, 5927. Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871. Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Lee, C.-S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279. MacCorquodale, F.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 347. Yadav, V.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 3283. Vite, G. D.; Alonso, R.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2268. Rajamannar, T.; Balasubramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 5789. Vijayabhaskar, K.; Subba Rao, G. S. R. *Tetrahedron Lett.* **1989**, *30*, 225. Srikrishna, A.; Hemamalini, P. (part 2 of this series), *J. Chem. Soc., Perkin Trans. 1* **1989**, 2511.

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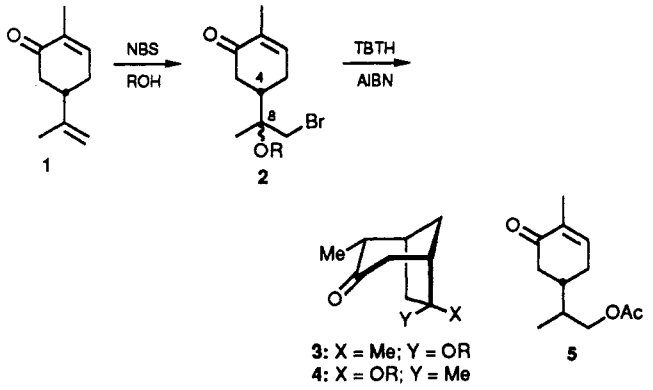
Table I. Bicyclo[3.2.1]octan-3-ones by Radical Cyclization Reaction

R	bromide	% yield	products	% yield[a]	$[\alpha]_D$[b] endo	$[\alpha]_D$[b] exo
Me	**2a**	76	**3a + 4a**	82	-21.8	-24.4
Et	**2b**	71	**3b + 4b**	60	-25.0	-15.0
$PhCH_2$	**2c**	60	**3c + 4c**	72	-29.1	-20.0
H	**2d**	76	**3d + 4d**	60	-21.8	-16.0
Ac	**2e**	50[c]	**3e + 4e + 5**	71	-12.5[d]	-25.0
Me	**11a**	79	**12a + 13a**	75	-15.0	-13.7
Ac	**11b**	46[c]	**12b + 13b**	73[e]	-32.0	10.0

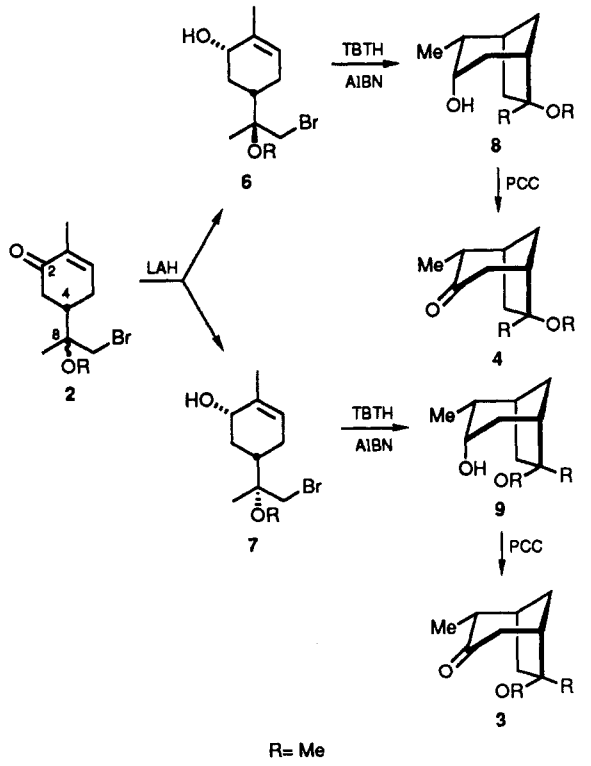
[a] Yields refer to isolated products (unoptimized). [b] Optical rotations were recorded in $CHCl_3$. [c] 25–40% of allylic bromination (at C-10) products were also obtained. [d] 2:1 mixture of **3e** and **5**. [e] 22% of 1,2-acetoxy-migrated product was also formed.

Scheme I

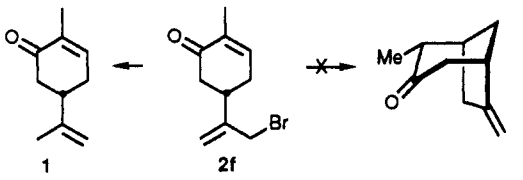


a, R = Me; **b**, R = Et; **c**, R = $PhCH_2$; **d**, R = H; **e**, R = Ac

Scheme II



also the regiospecificity, as the 6-endo mode of cyclization would have produced quaternary methyls. The stereochemical assignment at C-2 was derived from the ^{13}C NMR resonances of the C-2 methyl group (δ 12.7 for both **3a** and **4a**); the C-2 exo and endo methyls are known to resonate in the range of δ 18 and 12, respectively.[6] This assignment was further confirmed by the failure of **3a** or **4a** to undergo equilibration, indicating the stable equatorial (endo) orientation of the methyl group. The stereochemistry at C-6 was also derived from the ^{13}C NMR resonances of the C-6 methyl group carbon (δ 25.4 for **3a** and 19.0 for **4a**); the exo methyl is known to resonate at a lower field (δ 24) than the endo methyl (δ 15).[7] More conclusive evidence came from the chemical transformations outlined in Scheme II. To test the generality of this sequence, various bromides (**2b–f**), starting from (*S*)-carvone (1), were prepared and the radical cyclizations were carried out. The results are summarized in the Table I along with the optical rotations of the products. Thus, NBS bromination of 1 in the presence of ethanol, benzyl alcohol, and water generated the bromoenones **2b**, **2c**, and **2d**, in good yields. Bromination in the presence of acetic acid–sodium acetate furnished a mixture of the bromo enone **2e** and the allyl bromide **2f** in a 3:2 ratio. Bromo enones **2b–d** were cyclized to bicyclo[3.2.1]octan-3-ones **3b–d** and **4b–d** under the standard conditions (0.02 M, benzene, TBTH, 80 °C, AIBN) in good yields. Bromo enone **2e** gave about 20% of the acetoxy-migrated[8] product **5** in addition to the cyclized products **3e** and **4e**. Bromo enone **2f** failed to cyclize and gave only carvone (1) under a variety of conditions, including the more dilute conditions developed for the allyl radical cyclization by Stork and Reynolds (0.005 M).[9]



The observed cyclizations are undoubtedly facilitated by the presence of an electron-deficient olefin acceptor. To test this point, cyclizations were attempted with the corresponding alcohols **6** and **7**. These experiments also provided an unambiguous proof of the stereochemical assignment of **3** and **4** (Scheme II). Thus, lithium aluminum hydride (LAH) reduction[10] of the bromo enone **2a** at -50 °C furnished a cleanly separable mixture of 2*S*,4*S*,8*S* and 2*S*,4*S*,8*R* allylic alcohols **6** and **7**. Structures of **6** and **7** were derived from their ^1H and ^{13}C NMR spectra (see the Experimental Section). Stereochemical assignments were derived from further transformations. Conditions that result in cyclization of **2a** to **3a** and **4a** result only in reduction products with **6** and **7**. However, if the reaction is carried out at a concentration of 0.01 M, cyclized alcohols **8** and **9** are obtained in 60% yield. The structures of **8** and **9** were derived from their spectra, and

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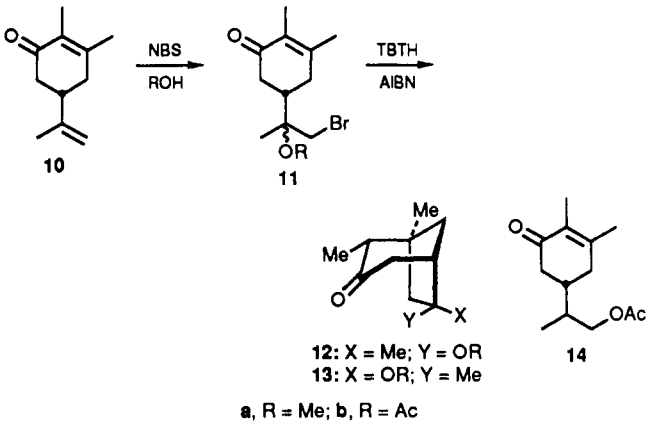
Scheme III



the stereochemical assignments were made on the basis of the IR spectra. Strong intramolecular hydrogen bonding was observed for **9** between the C-3 axial hydroxy and C-6 endo methoxy groups. This was confirmed by dilution experiments.[11] Oxidation of alcohol **8** furnished ketone **4a**. Analogously, oxidation of alcohol **9** gave ketone **3a**. Formation of ketones **3a** and **4a** from the alcohols **9** and **8** confirmed their assigned stereo structures.

The presence of a methyl group at the bicyclo[3.2.1]-octane bridgehead position in a number of natural products prompted us to extend this methodology to such systems. To this end, we chose (*S*)-6-methylcarvone (**10**), readily available[12] from (*R*)-carvone, as the starting material. Bromination of **10** in the presence of methanol generated the radical precursor **11a**. Bromination of **10** in the presence of sodium acetate–acetic acid furnished the acetoxy bromide **11b** along with the allylic bromination product (analogous to **2f**). Radical cyclization of **11a** furnished cleanly the bridgehead-substituted bicyclic compounds **12a** and **13a**, in 75% yield (Table I). As in the case of bromo enone **2e**, the bromide **11b** furnished 22% of the acetoxy-migrated uncyclized product **14** in addition to the cyclized products **12b** and **13b**. The structures of **12** and **13** were derived from comparison of their spectral data with those of **6** and **7**.

In conclusion, we have described here a new route to chiral bicyclo[3.2.1]octan-3-ones based on transannular radical cyclization. The cyclization of the unactivated systems **6** and **7** and the formation of the bridgehead substituted systems **12** and **13** clearly establish the versatility of this strategy.

Experimental Section

^{1}H NMR (60, 90, 270 MHz) and ^{13}C NMR (22.5 MHz) chemical shifts and coupling constants are reported in standard fashion (δ) with reference to internal tetramethylsilane (^{1}H NMR) or the central line (77.1 ppm) of $CDCl_3$ (^{13}C NMR). Off-resonance ^{13}C NMR multiplicities are given in parentheses. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. High- and low-resolution mass measurements were carried out with a JEOL JMS-DX 303 GC–MS instrument using a direct inlet mode. Optical rotations were measured with a Jobin-Vyon polarimeter using $CHCl_3$ as solvent. Analytical thin-layer chromatographies (TLC) were performed on (10 × 5 cm) glass plates coated with Acme's silica gel G (containing 13% calcium sulfate as binder) and various combinations of hexane and ethyl acetate (10:1 to 2:1) were used as eluents. Visualization of the spots was accomplished by exposure to iodine vapor. Acme's silica gel (100–200 mesh) was used for column chromatography. Solvent evaporations were done with a Büchi rotary evaporator or a steam bath. Dry ether and benzene were obtained by distillation from sodium and stored over pressed sodium wire. Dichloromethane was distilled from P_2O_5. Lithium aluminum hydride (LAH) and tri-*n*-butyltin hydride (TBTH) were obtained from Fluka, and *N*-bromosuccinimide (NBS) from E. Merck and were used without further purification. *N,N*-Azobisisobutyronitrile (AIBN) was crystallized from methanol and stored in the dark. The (*S*)-carvone used in this work had $[\alpha]_D$ +47° ($CHCl_3$).

5-(1-(Bromomethyl)-1-methoxyethyl)-2-methylcyclohex-2-enone (2a). A solution of (*S*)-carvone (1, 4.5 g, 30 mmol) in 45 mL of a 3:2 mixture of CH_2Cl_2–MeOH was cooled in an ice bath. To the magnetically stirring solution was added 6.4 g (36 mmol) of NBS in small portions over a period of 90 min. The mixture was stirred at room temperature for 20 h, diluted with 50 mL of CH_2Cl_2, washed with 0.5 M NaOH (3 × 20 mL), water (2 × 20 mL), and brine, and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure, and the residue was chromatographed on 80 g of silica gel. Elution with 1:3 ethyl acetate–hexane furnished the diastereomeric mixture of the bromo enone **2a** (6.4 g, 82%) as an oil. IR (neat): 1675, 910 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26 (3 H, s), 1.78 (3 H, s), 2.19–2.64 (5 H, m), 3.23 and 3.24 (3 H, s), 3.49, 3.42, and 3.44 (2 H, AB q and s, J = 11 Hz), 6.75 (1 H, br s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 198.9 and 198.5 (s), 144.7 and 143.7 (d), 134.7 and 134.5 (s), 75.4 (s), 49.2 and 49.0 (q), 40.5 (d), 38.6 and 37.8 (t), 36.4 (t), 26.5 and 25.7 (t), 17.4 (q), 15.1 (q). HRMS: $C_{11}H_{17}BrO_2$ requires 260.0412, found 260.0399.

5-(1-(Bromomethyl)-1-ethoxyethyl)-2-methylcyclohex-2-enone (2b). Bromination of (*S*)-carvone (1, 1.5 g, 10 mmol) with NBS (2.124 g, 12 mmol) in 15 mL of a 3:2 mixture of CH_2Cl_2–EtOH at ice temperature according to the foregoing procedure, followed by purification on 60 g of silica gel with 1:3 ethyl acetate–hexane as eluent, furnished a 1:1 diastereomeric mixture of the bromo enone **2b** (1.95 g, 71%) as an oil.

5-(1-(Bromomethyl)-1-(benzyloxy)ethyl)-2-methylcyclohex-2-enone (2c). Bromination of (*S*)-carvone (1, 4.5 g, 30 mmol) in 45 mL of a 3:2 mixture of CH_2Cl_2 and benzyl alcohol at ice temperature with NBS (6.4 g, 36 mmol) according to the foregoing procedure, followed by purification on 80 g of silica gel with 1:3 ethyl acetate–hexane as eluent, furnished a 1:1 diastereomeric mixture of bromo enone **2c** (6.06 g, 60%) as an oil. $[\alpha]_D$: +7.8° ($CHCl_3$).

5-(1-(Bromomethyl)-1-hydroxyethyl)-2-methylcyclohex-2-enone (2d). Bromination of (*S*)-carvone (1, 4.5 g, 30 mmol) in 45 mL of a 3:2 mixture of THF and water with NBS (6.4 g, 36 mmol) at 0 °C was carried out according to the procedure described for **2a**, for 22 h. The reaction mixture was saturated with solid NaCl and extracted with ether (3 × 30 mL). The ether extract was washed with water (2 × 20 mL) and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on 80 g of silica gel with 1:2 ethyl acetate–hexane as eluent furnished a 1:1 diastereomeric mixture of the hydroxy bromo enone **2d** (5.63 g, 76%)[13] as a viscous material. $[\alpha]_D$: −10.0° ($CHCl_3$).

5-(1-(Bromomethyl)-1-acetoxyethyl)-2-methylcyclohex-2-enone (2e). A solution of (*S*)-carvone (1, 4.5 g, 30 mmol) and sodium acetate (1.8 g, 22 mmol) in 45 mL of a mixture of CH_2Cl_2 and acetic acid was cooled in an ice bath. To the magnetically stirring solution was added 6.4 g (36 mol) of NBS in small portions over a period of 90 min. The reaction mixture was stirred at room temperature for 5 h, diluted with 50 mL of CH_2Cl_2, washed successively with water (3 × 30 mL), aqueous $NaHCO_3$ (3 × 30 mL), and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on 80 g of silica gel with 1:3 ethyl acetate–hexane as eluent furnished allyl bromide **2f** (1.25 g, 40%)[14] as an oil. IR (neat): 1670, 1110, 900 cm^{-1}. ^{1}H

(11) Dilution experiments were carried out in $CHCl_3$. An absorption due to free OH at 3640 cm^{-1} was observed for **8** in dilute solution, whereas no shift was observed for the OH band at 3450 cm^{-1} in the case of **9** on dilution. The assignments were further confirmed by Eu induced ^{1}H NMR shift studies. Upon addition of 0.17 equiv of Eu(fod)$_3$, the methoxy signal of **9** shifted more (0.56 ppm) than that of **8** (0.28 ppm).

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(14) Kato, T.; Ichinose, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1051.

NMR (60 MHz, CCl_4): δ 1.73 (3 H, s), 2.1–3.2 (5 H, m), 3.96 (2 H, s), 5.05 (1 H, d, J = 2 Hz), 5.3 (1 H, d, J = 2 Hz), 6.65 (1 H, br s). Further elution of the column furnished a diastereomeric mixture of the acetoxy bromo enone **2e** (4.33 g, 50%) as an oil.

6-Methoxy-2,6-dimethylbicyclo[3.2.1]octan-3-one (3a and 4a). A solution of bromo enone **2a** (261 mg, 1 mmol), tributyltin hydride (0.3 mL, 1.1 mmol), and AIBN (catalytic) in 55 mL of benzene was refluxed for 3 h. The reaction mixture was cooled, washed with 1% aqueous NH_4OH (3 × 20 mL) and brine, and dried over Na_2SO_4. Solvent was removed under reduced pressure, and the residue was chromatographed on 15 g of silica gel. Elution first with hexane to remove the tin byproducts and then with 1:3 ethyl acetate–hexane and careful pooling of fractions furnished the cyclized products **3a** and **4a** (1:1, 150 mg, 82%) as oils. These were distilled bulb-to-bulb (bath temperature 120 °C/5 Torr).

Compound **3a**. IR (neat): 1700, 1370, 1200, 1060, 870 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 1.03 (3 H, d, J = 7 Hz, C-2 Me), 1.3 (3 H, s, C-6 Me), 1.52–2.69 (9 H, m), 3.17 (3 H, s, OMe). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 211.4 (s, C=O), 84.0 (s, *C*-OMe), 51.3 (2C, d and q, *C*H-C=O and OMe), 45.5 (d), 43.9 (t), 40.3 (d), 38.3 (t), 37.7 (t), 25.4 (q, C-6 Me), 12.7 (q, C-2 Me). HRMS: $C_{11}H_{18}O_2$ requires 182.1307, found 182.1335.

Compound **4a**. IR (neat): 1700, 1370, 1210, 1180, 1080, 870 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.99 (3 H, d, J = 7 Hz, C-2 Me), 1.19 (3 H, s, C-6 Me), 1.2–2.5 (9 H, m), 3.14 (3 H, s, OMe). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 212.5 (s, C=O), 84.9 (s, *C*-OMe), 51.5 (d, *C*-2), 49.2 (q, OMe), 45.2 (t), 44.3 (d), 41.2 (d), 39.2 (t), 37.7 (t), 19.0 (q, C-6 Me), 12.7 (q, C-2 Me). HRMS: $C_{11}H_{18}O_2$ requires 182.1307, found 182.1300.

6-Ethoxy-2,6-dimethylbicyclo[3.2.1]octan-3-one (3b and 4b). Radical cyclization of bromo enone **2b** (275 mg, 1 mmol) in 55 mL of benzene with TBTH (0.3 mL, 1.1 mmol) in the presence of AIBN (catalytic) as described for **2a** and purification over 15 g of silica gel furnished the cyclized products **3b** and **4b** (1:1, 117 mg, 60%). These were further purified by bulb-to-bulb distillation (bath temperature 120 °C/5 Torr).

6-(Benzyloxy)-2,6-dimethylbicyclo[3.2.1]octan-3-one (3c and 4c). Radical cyclization of bromo enone **2c** (337 mg, 1 mmol) in 55 mL of benzene with TBTH (0.3 mL, 1.1 mmol) and AIBN (catalytic) as described for **2a** and purification over 15 g of silica gel furnished the cyclized products **3c** and **4c** (1:1, 185 mg, 72%). These were further purified by bulb-to-bulb distillation (bath temperature 170 °C/20 Torr).

6-Hydroxy-2,6-dimethylbicyclo[3.2.1]octan-3-one (3d and 4d). Radical cyclization of bromo enone **2d** (247 mg, 1 mmol) in 55 mL of benzene with TBTH (0.3 mL, 1.1 mmol) and AIBN (catalytic) for 3 h and purification over 15 g of silica gel with 1:2 ethyl acetate–hexane as eluent furnished the cyclized products **3d** and **4d** (1:1, 100 mg, 60%) as viscous materials.

6-Acetoxy-2,6-dimethylbicyclo[3.2.1]octan-3-one (3e and 4e). Radical cyclization of bromo enone **2e** (289 mg, 1 mmol) in 55 mL of benzene with TBTH (0.3 mL, 1.1 mmol) and AIBN (catalytic) for 3 h and purification over 10 g of silica gel with 1:3 ethyl acetate–hexane furnished acetoxy-migrated enone **5** (45 mg, 21%). IR (neat): 1730, 1630 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 0.98 (3 H, d, J = 6 Hz), 1.76 (3 H, s), 1.98 (3 H, s), 1.8–2.78 (5 H, m), 3.9 (2 H, m), 6.6 (1 H, br s). Further elution of the column furnished the cyclized products **3e** and **4e** (1:1, 150 mg, 71%).

Radical Reaction of Bromo Enone 2f. A solution of bromo enone **2f** (60 mg, 0.26 mmol), TBTH (0.078 mL, 0.28 mmol), and AIBN (catalytic) in 58 mL of benzene was refluxed for 3 h. Usual workup as described earlier and purification over 5 g of silica gel furnished carvone (**1**, 27 mg, 70%) and was identified by comparison (IR, ^1H NMR) with an authentic sample.

(1*S*,5*S*,8*S*)- and (1*S*,5*S*,8*R*)-5-(1-(Bromomethyl)-1-methoxyethyl)-2-methylcyclohex-2-en-1-ols (6 and 7). A solution of bromo enone **2a** (1.47 g, 5.63 mmol) in 25 mL of dry ether was cooled (−50 °C) in an ethanol–liquid N_2 bath. To the magnetically stirring solution was added 260 mg (6.8 mmol) of LAH in one portion. The reaction mixture was stirred at the same temperature for 2 h and slowly warmed to −10 °C, and 1 mL of ethyl acetate was slowly introduced to consume the excess LAH. The reaction was quenched with 5 mL of ice-cold water and 25 mL of 10% aqueous sulfuric acid and stirred at room temperature for 10 min. The ether layer was separated, and the aqueous layer was extracted with more ether (3 × 30 mL). The combined ether extract was washed with aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. Solvent was removed, and the residue was chromatographed on 30 g of silica gel with 1:3 ethyl acetate–hexane. Careful mixing (by TLC) of the fractions furnished the two alcohols **6** and **7** (1:1, 1.36 g, 92%) as oils.

Compound **6**. $[\alpha]_D$: −3.8° ($CHCl_3$). IR (neat): 3380, 1380, 1200, 920 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.2 (3 H, s), 1.75 (3 H, s), 1.6–2.4 (5 H, m), 3.24 (3 H, s), 3.54 and 3.31 (2 H, AB q, J = 14 Hz), 4.2 (1 H, br s), 5.45 (1 H, br s). ^{13}C NMR (22.5 MHz, $CDCl_3$): 137.2 (s), 122.2 (d), 76.1 (s), 70.0 (d), 48.7 (q), 38.6 (d), 37.2 (t), 32.9 (t), 26.5 (t), 18.6 (q), 16.8 (q). HRMS: $C_{11}H_{19}BrO_2$ requires 262.0569, found 262.0579.

Compound **7**. $[\alpha]_D$: 0° ($CHCl_3$). IR (neat): 3380, 1380, 1090, 930 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.2 (3 H, s), 1.7 (3 H, s), 1.9–2.2 (5 H, m), 3.25 (3 H, s), 3.45 (2 H, s), 4.2 (1 H, br s), 5.5 (1 H, br s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 136.3 (s), 123.1 (d), 76.2 (s), 70.2 (d), 48.9 (q), 38.6 (d), 37.8 (t), 34.1 (t), 25.9 (t), 18.5 (q), 17.8 (q). HRMS: $C_{11}H_{19}BrO_2$ requires 262.0569, found 262.0579.

3-*endo*,6-*exo*-6-Methoxy-2,6-dimethylbicyclo[3.2.1]octan-3-ol (8). Radical cyclization of bromo alcohol **6** (132 mg, 0.5 mmol) in 55 mL of benzene with TBTH (0.15 mL, 0.55 mmol) and AIBN (catalytic) as described for **2a** and purification over 10 g of silica gel with 1:2 ethyl acetate–hexane as eluent furnished the cyclized alcohol **8** (55 mg, 60%) as an oil. $[\alpha]_D$: −2.85° ($CHCl_3$). IR ($CHCl_3$): 3640, 3480, 1380, 1190, 1090, 970 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 0.98 (3 H, d, J = 7 Hz), 1.5 (3 H, s), 1.1–2.4 (9 H, m), 3.15 (3 H, s), 3.9 (1 H, br s), 1.35 (1 H, s, exchanged with D_2O). HRMS: $C_{11}H_{20}O_2$ requires 184.1463, found 184.1459.

3-*endo*,6-*endo*-6-Methoxy-2,6-dimethylbicyclo[3.2.1]octan-3-ol (9). Radical cyclization of bromo alcohol **7** (132 mg, 0.5 mmol) in 55 mL of benzene with TBTH (0.15 mL, 0.55 mmol) and AIBN (catalytic) for 3 h as described for **2a** and purification over 10 g of silica gel with 1:3 ethyl acetate–hexane as eluent furnished the cyclized alcohol **9** (55 mg, 60%) as an oil. $[\alpha]_D$: −33.3° ($CHCl_3$). IR ($CHCl_3$): 3440, 1380, 1240, 1170, 1060, 970 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.0 (3 H, d, J = 7 Hz), 1.35 (3 H, s), 1.2–2.4 (9 H, m), 3.3 (3 H, s), 3.7 (1 H, br s), 4.8 (1 H, br s, exchanged with D_2O). HRMS: $C_{11}H_{20}O_2$ requires 184.1463, found 184.1496. Further elution of the column furnished starting bromo alcohol **7** (20 mg, 22%).

PCC Oxidation of the Alcohol 8. To a suspension of PCC (162 mg, 0.75 mmol) and sodium acetate (82 mg, 1 mmol) in 5 mL of CH_2Cl_2 was added a CH_2Cl_2 (2 mL) solution of the alcohol **8** (132 mg, 0.5 mmol) in one portion. The reaction mixture was vigorously stirred at room temperature for 2 h. The entire reaction mixture was charged on 10 g of silica gel and eluted with more methylene chloride to furnish the ketone **4a** (124 mg, 95%) and was identified by comparison with the sample obtained earlier.

PCC Oxidation of the Alcohol 9. Oxidation of the alcohol **9** (61 mg, 0.25 mmol) with PCC (81 mg, 0.375 mmol) and sodium acetate (41 mg, 0.5 mmol) in CH_2Cl_2 (7 mL) for 2 h and purification on 10 g of silica gel furnished the ketone **3a** (56 mg, 95%), which was identified by comparison with the sample obtained earlier.

5-(1-(Bromomethyl)-1-methoxyethyl)-2,3-dimethylcyclohex-2-en-1-one (11a). A solution of methylcarvone **10** (1.64 g, 10 mmol)[12] in 20 mL of a 3:2 mixture of CH_2Cl_2–MeOH was cooled in a freezing bath (−10 °C). To the magnetically stirring solution was added 2.14 g (12 mmol) of NBS in small portions over a period of 35 min. The reaction mixture was stirred at room temperature for 22 h and worked up as described for **2a**. Purification over 40 g of silica gel with 1:3 ethyl acetate–hexane furnished the 1:1 diastereomeric mixture of the bromo enone **11a** (2.17 g, 79%) as a thick viscous oil. $[\alpha]_D$: −45.7° ($CHCl_3$).

5-(1-(Bromomethyl)-1-acetoxyethyl)-2,3-dimethylcyclohex-2-en-1-one (11b). A solution of the methylcarvone **10** (984 mg, 6 mmol)[12] and sodium acetate (500 mg, 6.1 mmol) in 55 mL of a 10:1 mixture of CH_2Cl_2 and acetic acid was cooled in a freezing bath (−10 °C). To the magnetically stirring solution, was added 1.27 g (7.2 mmol) of NBS in small portions over a period of 20 min. The reaction mixture was stirred for 5 h at room temperature, and usual workup as described earlier for **2e** and purification over 30 g of silica gel with 1:3 ethyl acetate–hexane furnished first 10-bromo-6-methylcarvone (365 mg, 26%) as an oil. IR (neat): 1660, 1385, 920 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 1.7 (3 H, s),

1.93 (3 H, s), 2.3–2.6 (5 H, m), 3.93 (2 H, s), 5.0 (1 H, s), 5.23 (1 H, s). HRMS: $C_{11}H_{15}O$ (M^+ – Br) requires 163.1123, found 163.1157. Further elution of the column furnished a 2:1 diastereomeric mixture of the acetoxy bromo enones **11b** (806 mg, 46%) as an oil.

6-Methoxy-1,2,6-trimethylbicyclo[3.2.1]octan-3-one (12a and 13a). Radical cyclization of bromo enone **11a** (275 mg, 1 mmol) in 55 mL of benzene with TBTH (0.3 mL, 1.1 mmol) and AIBN (catalytic) for 1.5 h as described for **2a** and purification over 15 g of silica gel furnished the cyclized compounds **12a** and **13a** (1:1, 146 mg, 75%) as oils. These were further purified by bulb-to-bulb distillation (bath temperature 135 °C/10 Torr).

6-Acetoxy-1,2,6-trimethylbicyclo[3.2.1]octan-3-one (12b and 13b). Radical cyclization of bromo enone **11b** (303 mg, 1 mmol) in 55 mL of benzene with TBTH (0.3 mL, 1.1 mmol) and AIBN (catalytic) for 1.5 h and purification over 15 g of silica gel with 3:1 ethyl acetate–hexane as eluent furnished first the acetoxy-migrated product **14** (50 mg, 22%) as an oil. IR (neat): 1740, 1670, 1380, 1240, 1040 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 0.95 (3 H, d, J = 6.5 Hz), 1.7 (3 H, s), 1.92 (3 H, s), 2.0 (3 H, s), 2.0–2.4 (5 H, m), 3.9 (2 H, m). Further elution of the column furnished the cyclized acetates **12b** and **13b** (163 mg, 73%) as oils. These were further purified by bulb-to-bulb distillation (bath temperature 155 °C/10 Torr).

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Registry No. 1, 2244-16-8; **2a** (isomer 1), 127400-19-5; **2a** (isomer 2), 127400-27-5; **2b** (isomer 1), 127400-33-3; **2b** (isomer 2), 127400-35-5; **2c** (isomer 1), 127400-29-7; **2c** (isomer 2), 127400-36-6; **2d** (isomer 1), 127400-30-0; **2d** (isomer 2), 127400-37-7; **2e** (isomer 1), 127400-31-1; **2e** (isomer 2), 127400-38-8; **2f**, 127400-26-4; **3a**, 127470-66-0; **3b**, 127400-34-4; **3c**, 127400-39-9; **3d**, 127470-74-0; **3e**, 127470-75-1; **4a**, 127470-67-1; **4b**, 127470-71-7; **4c**, 127470-72-8; **4d**, 127400-42-4; **4e**, 127400-43-5; **5**, 127400-20-8; **6**, 127400-21-9; **7**, 127470-68-2; **8**, 127400-22-0; **9**, 127470-69-3; **10**, 85710-66-3; **11a** (isomer 1), 127400-23-1; **11a** (isomer 2), 127400-32-2; **11b** (isomer 1), 127400-28-6; **11b** (isomer 2), 127400-40-2; **12a**, 127400-24-2; **12b**, 127400-41-3; **13a**, 127470-70-6; **13b**, 127470-73-9; **14**, 127400-25-3.

Supplementary Material Available: Spectral data and HRMS (or analytical data) for the compounds **2b–e**, **3b–e**, **4b–e**, **11a–b**, **12a–b**, and **13a–b** (4 pages). Ordering information is given on any current masthead page.

The Development of a New Nitrating Agent: The Unusual Regioselective Nitration of Diphenylpolyethylene Glycols and Phenylpolyethylene Glycols with Trimethylsilyl Nitrate–BF_3OEt_2

Masaru Kimura,* Kazushige Kajita, Naoyuki Onoda, and Shiro Morosawa

Department of Chemistry, Faculty of Science, Okayama University, Tsushimanaka-3-1-1, Okayama 700, Japan

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We have investigated the nitration of the following podands, 1-phenoxy-8-(2′-nitrophenoxy)-, 1-phenoxy-8-(4′-nitrophenoxy)-, and 1-(2′,4′-dinitrophenoxy)-8-phenoxy-3,6-dioxaoctane (**1**, **2**, and **3**), and 1-(2′,4′-dinitrophenoxy)-11-phenoxy-3,6,9-trioxaundecane (**4**), 1-phenoxy-3,6,9-trioxadecane (**5**), and 1-phenoxy-3,6,9,12-tetraoxatridecane (**6**), with trimethylsilyl nitrate catalyzed by BF_3OEt_2, which is soluble in nonpolar solvents. The reaction selectivity was measured by the ortho:para ratio of the nitrated products and was unusually large in CCl_4. The structures of all isolated products, 1,8-bis(2′-nitrophenoxy)-, 1-(2′-nitrophenoxy)-8-(4′-nitrophenoxy)-, 1,8-bis(4′-nitrophenoxy)-, 1-(2′,4′-dinitrophenoxy)-8-(2′-nitrophenoxy)-, and 1-(2′,4′-dinitrophenoxy)-8-(4′-nitrophenoxy)-3,6-dioxaoctane (**7**, **8**, **9**, **10**, and **11**), 1-(2′,4′-dinitrophenoxy)-11-(2′-nitrophenoxy)- and 1-(2′,4′-dinitrophenoxy)-11-(4′-nitrophenoxy)-3,6,9-trioxaundecane (**12** and **13**), 1-(2′-nitrophenoxy)- and 1-(4′-nitrophenoxy)-3,6,9-trioxadecane (**14** and **15**), and 1-(2′-nitrophenoxy)- and 1-(4′-nitrophenoxy)-3,6,9,12-tetraoxatridecane (**16** and **17**), were confirmed by the independent preparation of these compounds using a modification of Joeger's method. We have invented a new nitrating system (trimethylsilyl nitrate and BF_3OEt_2) and have shown that the selectivity (o/p ratio of nitrated products) is unusually high in CCl_4.

There have been several reports in the literature concerning aromatic nitration with unusual positional selectivity using naked nitronium ion generated in polar solvents.[1,2] Nonpolar solvents are usually preferable for the generation of naked nitronium ion, but examples of well-controlled aromatic nitrations in nonpolar solvents are rare.[1b] The nitrating agents commonly used are nitric acid in the presence of other acids, nitronium salts,[3] and nitrate esters.[1b,4,6] The nitronium ion (NO_2^+) generated from these agents is known to exist as a solvated species in most aromatic nitrations. When these reagents are used in solvents with heteroatoms, the reactivity and selectivity vary with the size of the solvated nitronium ion. In particular, it has been found that the interaction between nitronium ions and oxygen atoms is an important consideration in regioselective nitrations. For example, Olah et al. recorded the highest ortho selectivity (ortho/para ratio = o/p = 2.7 or 3.0) in the nitrations of anisole with NO_2PF_6–OEt_2 and *N*-nitro-2,4,6-collidinium tetrafluoroborate, respectively.[1,5] Benzene derivatives with properly placed oxygen atoms in side chains seem to promote the

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