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FREE RADICAL REARRANGEMENT OF BICYCLO[2.2.2]- AND BICYCLO[4.2.0]OCTENONE SYSTEMS

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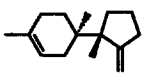
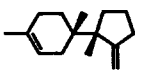
Abstract: *Intramolecular cyclization of carbon radicals to carbonyl groups was carried out on bicyclo[2.2.2]- and bicyclo[4.2.0]octenones. An unexpected ring expansion product* **19**, *produced by β-scission of the intermediate alkoxyl radical* **22**, *was observed. The β,γ-situated double bond of the bicyclic ketones appears to have a dampening effect on the carbon radical-ketone cyclization and the allylic cleavage of the alkoxyl radical.*

Introduction

Radical cyclization has been developed in this laboratory as a new method for ring expansion.[1,2] The method involves the addition of carbon radicals to carbonyl groups[3] and leads to intermediate oxy radicals. Recently, we have been exploring an extension of this strategy to bicyclo[2.2.2]- and bicyclo[4.2.0]octenones, intended to lead to stereoselective syntheses of the diastereomeric natural products (±)-trichodiene (**1**) and (±)-bazzanene (**2**). Numerous synthetic approaches to these substances have been reported in the literature.[4]

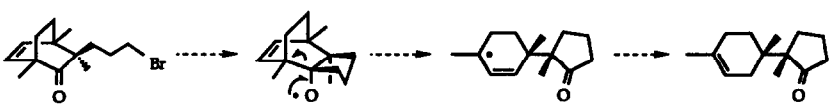


1
(±)-trichodiene



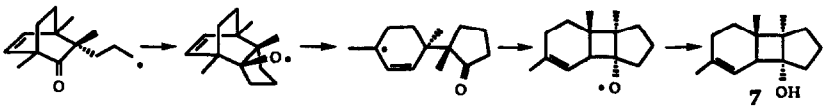
2
(±)-bazzanene

Our intent was to explore free radical addition to the carbonyl group of the bicyclic ketone **3** (eq 1). We anticipated that radical addition might be followed by ring cleavage of the oxy radical



3-exo **4** **5** **6** (1)

4, yielding the allylic radical **5**, then the enone precursor **6** to (±)-bazzanene (**2**). We wanted to learn whether the incipient allyl radical would provide sufficient driving force for ring opening, as had the ester group in our earlier ring expansion studies.[1f-k] Further interest attached to this question because Snowden *et al.* [5] had suggested a free radical path to explain the formation of a minor product **7** (eq 2), formed in the course of work leading to (±)-trichodiene (**1**). We have

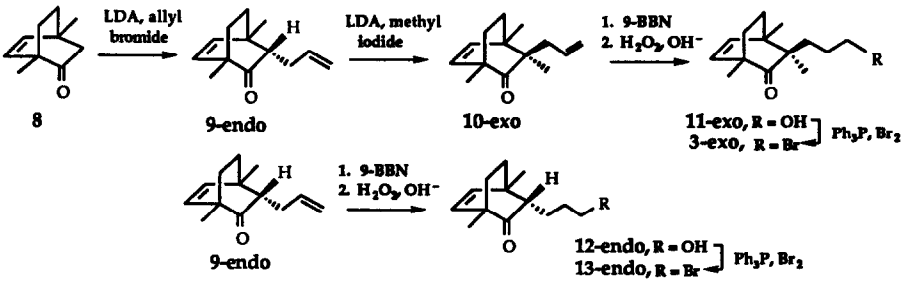


(2)

confirmed the observation of 7, and we have proposed a new mechanism for its formation based on single and double electron transfer sequences.[6]

Results and Discussion

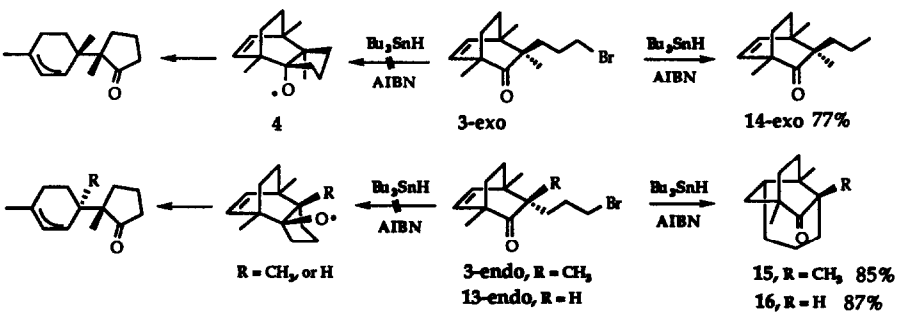
The exo diastereomer **3-exo**, leading to (±)-bazzanene (**2**), is readily prepared by alkylating the bicyclic ketone **8** (eq 3a),[7] first with allyl bromide then with methyl iodide.[5] The propene



(3a)

(3b)

sidechain in **10-exo** is then converted to the bromopropyl group yielding **3-exo**. When tin hydride-promoted free radical addition to the carbonyl group of **3-exo** was attempted, the reduction product **14-exo** was produced (eq 4a). In this instance, hydrogen transfer from tin



(4a)

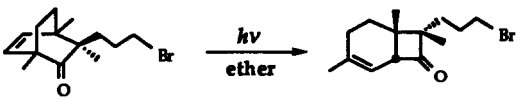
(4b)

hydride is apparently faster than addition to the ketone, even under conditions of slow addition of the reagent with a syringe pump. Alternatively, addition of the sidechain radical to the carbonyl group might occur yielding the oxy radical **4**, but be reversible and not lead to the desired product because of slow allylic carbon-carbon bond cleavage *(vide infra)*.

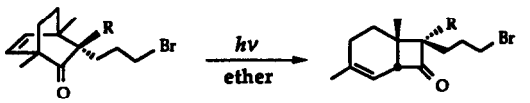
The endo diastereomer **3-endo** was prepared by changing the alkylation sequence. Radical generation from **3-endo** permitted us to study the competition for cyclization between the carbon-carbon double bond and the ketone (eq 4b). Failure to observe **7** and an 85% isolated yield of olefin addition product **15** indicate that radical addition to the carbonyl group in **3-endo** is not

competitive with cyclization to the carbon-carbon double bond.[8] Accordingly, this result is not consistent with the free radical mechanism shown in eq 2.[5]

In pursuit of an alternative strategy, the bicyclo[4.2.0]octenones **17-endo** and **17-exo** were prepared stereospecifically by photochemical 1,3-acyl shift[9] of the bicyclo[2.2.2]octenones **3-exo** and **3-endo** (eq 5a and 5b). The four-membered ketone in **17-exo** provides a substantially more



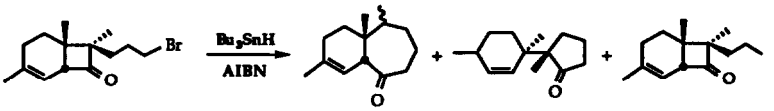
3-exo **17-endo** (5a)



3-endo, R = CH_3
13-endo, R = H
17-exo, R = CH_3
18-exo, R = H (5b)

reactive carbonyl group than that in **3-exo** and should provide a better opportunity to observe radical addition to the ketone followed by the desired fragmentation.

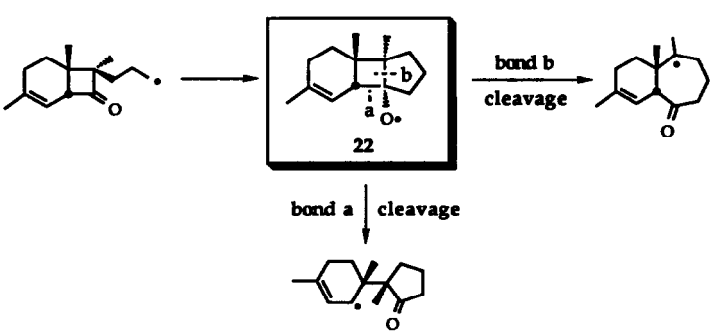
When the new bromide, **17-exo**, was treated with Bu_3SnH, very little (11%) of the expected opening to **20** occurred. Far more interesting, *the major product of the reaction, formed in 80% relative yield (isolated yield 69%), was the seven-membered ring product* **19** *resulting from cleavage of the central carbon-carbon bond and leading to ring expansion* (eq 6a). This was not



17-exo **19** 80% **20** 11% **21-exo** 9% (6a)

the expected result. In the alkoxy radical intermediate **22** leading to ring expansion, it was surprising to find that bond **b** cleaved in preference to bond **a** (Scheme 1). Both bond scissions

Scheme 1

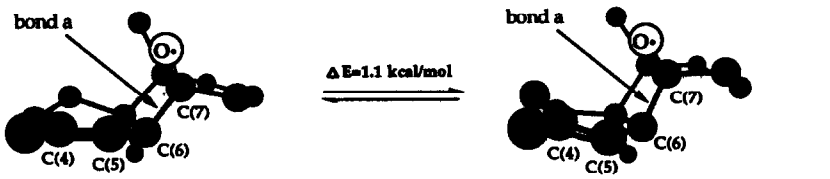


result in relief of strain in the cyclobutane ring, but bond a is allylic, and it was expected to be the main site of bond cleavage. An MM2 calculation[10] reveals that **19** and **20** are about equally strained, with **19** being approximately 1 kcal/mole the less stable of the two. Tin hydride treatment of **17-endo** yielded only direct reduction product **21-endo** (eq 6b), a consequence of steric hindrance to ring closure.

17-endo 21-endo (6b)

Examination of models[10a] reveals two conformations of the presumed intermediate oxy radical **22** (Scheme 2). In the more extended, and presumably more stable intermediate,

Scheme 2. Conformations of Oxy Radical 22

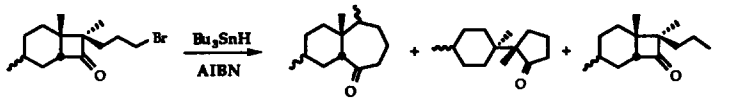


C(4)-C(5)-C(6)-C(7) Dihedral Angle: 116.5° C(4)-C(5)-C(6)-C(7) Dihedral Angle: 81.2°

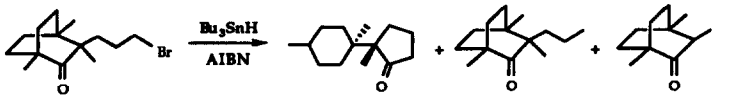
Conformation A of 22 **Conformation B of 22**

A, the allylic carbon-carbon bond **a** is canted at a less favorable angle (116.5°) with respect to the π-bond than it is in conformation **B** (81.2°). The obliqueness of the angle in conformation **A** may be such as to allow cleavage of bond **b** in preference to bond **a** (Scheme 1).

When the double bond in **3-exo** is removed to give **23-exo**, treatment of the latter with Bu_3SnH yields *more* bond **a** cleavage product (eq 7, relative yields are shown). This is also true



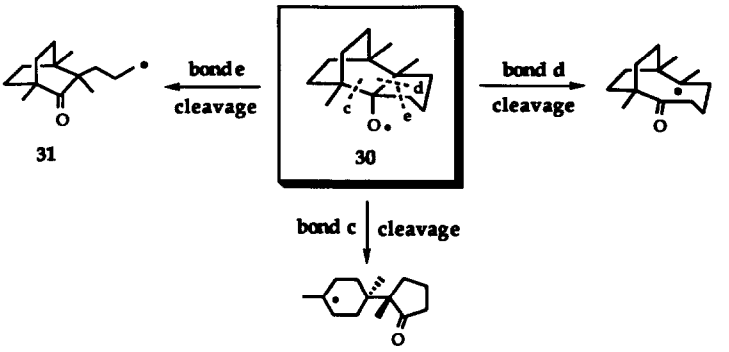
23-exo **24** 68% **25** 22% **26-exo** 10% (7)



27 **25** (1 diastereomer) 53% **28** 24% **29** 11% (8)

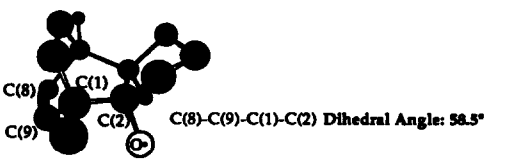
in the bicyclo[2.2.2] series. Hydrogenation of the double bond of **11** yields **27**. Free radical generation by treatment of **27** with Bu_3SnH leads to radical addition to the carbonyl group affording 53% cleavage (relative yield) of ring bond **c** (eq 8 and Scheme 3). In both **3-exo** and **17-exo** the double bond has an apparent dampening effect on the reactivity of the carbonyl group.

Scheme 3



Perhaps this is an inductive deactivation. With an angle of 58.5° the stereoelectronic situation in the oxy radical **4** (Scheme 4), a possible intermediate from radical reaction of bicyclo[2.2.2]-

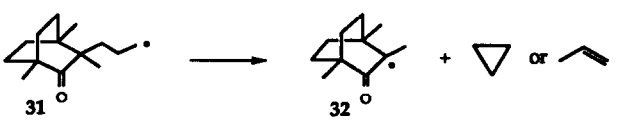
Scheme 4



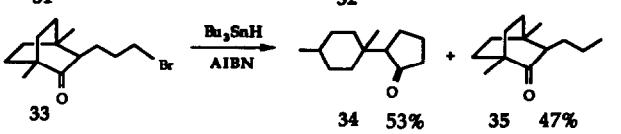
Oxy Radical 4

octenone **3-exo**, can be judged to be not very favorable for ring cleavage toward the allylic radical.

In the reaction of **27** an unexpected minor product **29** (eq 8) was observed. The α-methyl ketone **29** is apparently derived by fragmentation of the initial primary radical **31** leading to the



(9)

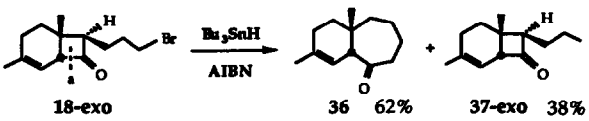


(10)

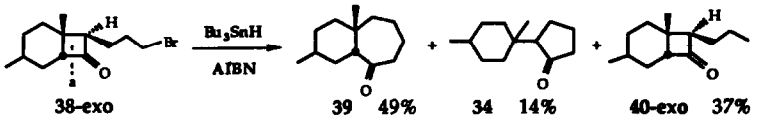
acyl substituted tertiary radical **32**, while a three carbon piece is lost (cyclopropane or propene) (eq 9). We know of no precedent for such a transformation. No analogous product is detected from the reaction of **33** (eq 10).

We also examined the effect of removing the angular methyl group in **17-exo** so that ring opening of **18-exo** would yield a secondary radical in competition with cleavage to the allylic

radical. Once again we observed only ring expansion and direct reduction, *with no cleavage toward the allylic center* (eq 11a). This result shows that the methyl group has little impact on



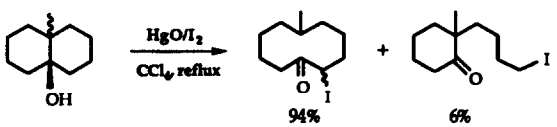
(11a)



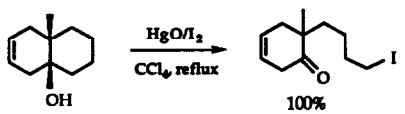
(11b)

the cleavage of bond a. However, when the double bond is removed in **38-exo**, 14% of bond a cleavage product was detected (eq 11b). This reinforces the notion that the double bond may have a deactivating effect on the cleavage of bond a.

MacDonald examined the β-scission of alkoxyl radicals[11,12] from thermolysis of *in situ*-generated hypohalites of fused-ring tertiary hydroxyl systems (eqs 12 and 13), finding that



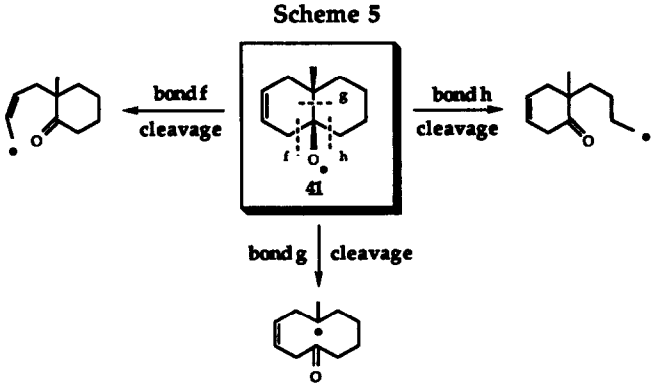
(12)



(13)

cleavage also occurred away from the allylic carbon-carbon bond (Scheme 5). This is more easily

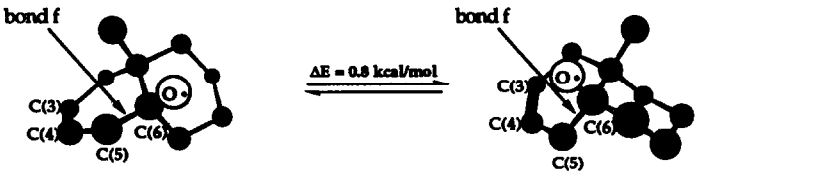
Scheme 5



understood than is the small extent of allylic cleavage in **18-exo**. Examination of models shows that in both conformations of the oxy radical **41** the allylic carbon-carbon σ-bonds **f** are oriented at an unfavorable angle (14.8° for conformation **A**, 13.8° for conformation **B**) with respect to the

π-bond (Scheme 6).

Scheme 6. Conformations of Oxy Radical 41



C(3)-C(4)-C(5)-C(6) Dihedral Angle: 14.8°

Conformation A of 41

C(3)-C(4)-C(5)-C(6) Dihedral Angle: 13.8°

Conformation B of 41

Conclusion

Exploration of bicyclo[2.2.2]- and bicyclo[4.2.0]octenone systems has led to the discovery of an unusual β-scission of an alkoxyl radical. The carbon-carbon double bond of the β,γ-unsaturated ketone appears to have a negative impact on both the radical-ketone cyclization and subsequent allylic cleavage of the alkoxyl radical. Nonetheless, this unexpected outcome is consistent with our ring expansion goals, and that inquiry now forms an important part of our research into the ring expansion of cyclobutanone-containing systems.[1a-e]

Experimental Section

Materials and Methods. All reactions were performed under a nitrogen atmosphere. Tetrahydrofuran (THF), benzene, and diethyl ether were distilled from blue or purple solutions of sodium benzophenone ketyl under nitrogen immediately prior to use. A 1.5 M solution of lithium diisopropylamide (LDA) in THF and a 0.5 M solution of 9-borabicyclo[3.3.1]nonane (9-BBN) in THF (Aldrich) were used without further purification.

^{1}H and ^{13}C NMR spectra were obtained on Bruker AC-300, or IBM AF-300 spectrometers (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR). J values are given in Hz. Infrared (IR) spectra were obtained on an IBM IR/32 FTIR or a Mattson Cygnus 100 FTIR spectrometer. Gas chromatography and low resolution mass spectra (GC-MS) were obtained from a Hewlett-Packard (5890 series II) gas chromatograph equipped with a Hewlett-Packard (5970 series) mass spectrometer. The GC column was a 12 m x 0.2 mm I.D. x 0.33 μm film thickness fused silica capillary column with 100% dimethyl polysiloxane (HP-1, Hewlett-Packard). Relative yields and ratios of diastereomers were determined on GC. High-Resolution mass spectra were obtained on a Varian MAT CH-5DF, or a VG-70G spectrometer. The purity of products isolated as single compounds was determined by GC or ^{1}H NMR.

1,4-Dimethylbicyclo[2.2.2]oct-5-en-2-one (8). A simple and efficient procedure for the preparation of 8 was developed.[7] It relies on Diels-Alder trapping of 1,3-cyclohexadiene formed by acid-catalized isomeriation of 1,4-cyclohexadiene and avoids the tedious isolation of the former from the equilibrium mixture of the 1,3- and 1,4-isomer. Thus, crude 1,4-dimethyl-1,4-cyclohexadiene (9.6 g, 79% pure), prepared by Birch reduction of *p*-xylene, and α-chloro-acrylonitrile (12.4 g, 140 mmol), in 15 ml of *p*-xylene containing hydroquinone (0.1 g), was mixed with a solution of 36% HCl (5 mL) in water (36 mL). The mixture was heated at 100°C over a period of 5 days. Flash chromatography (10:1 hexanes-ether) after ether workup gave the Diels-

Alder adduct as an 8:1 diastereomeric mixture (11.2 g, 81%). A portion of Diels-Alder adduct (4.0 g, 20 mmol) and $NaS{\cdot}9H_2O$ (24.6 g, 100 mmol) in EtOH (50 mL) was stirred at reflux for 40 h. Flash chromatography (30:1 hexanes-ether) after ether workup gave **8** as a colorless liquid (2.5 g, 83%). The ^1H NMR, IR, and MS spectra of **8** are in good agreement with the reported values.[5b]

Compounds **9-endo, 10-exo, 10-endo, 11-exo, 11-endo, and 12-endo** were prepared following literature methods.[5b]

General procedures for the bromination of alcohols: (1SR,3RS,4RS)-3-(3'-Bromopropyl)-1,3,4-trimethylbicyclo[2.2.2]oct-5-en-2-one (3-exo). A 0.1 M solution of Br_2 in pyridine was added dropwise to a solution of **11-exo** (100 mg, 0.45 mmol) and triphenylphosphine (200 mg, 0.76 mmol) in pyridine (5 mL) at 0°C. The addition of Br_2 was continued until the mixture was an orange tint, then 10% aq. HCl (8 mL) was added to the reaction mixture. Flash chromatography (20:1 hexanes-ether) of the crude product after ether workup gave **3-exo** as a colorless oil (102 mg, 80%). ^1H NMR ($CDCl_3$) δ 1.01 (s, 3 H), 1.16 (s, 3 H), 1.17 (s, 3 H), 1.20-1.55 (3 H), 1.62 (m, 2 H), 1.88 (m, 2 H), 2.17 (M, 1 H), 3.38 (m, 2 H), 5.17 (d, J=8.1, 1 H), 6.13 (d, J=8.1, 1 H). ^{13}C NMR ($CDCl_3$) δ 18.2 (q, J=127), 19.4 (q, J=126), 22.1 (q, J=128), 27.8 (t, J=128), 29.9 (t, J=131), 30.7 (t, J=129), 32.8 (t J=128), 35.2 (t, J=147), 43.8 (s), 47.7 (s), 49.0 (s), 131.0 (d, J=168), 144.3 (d, J=163), 216.0 (s). IR (neat) 1712 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 286 and 284 (<1, M^+), 161 (4), 135 (6), 108 (100, M^+-$C_6H_9{}^{79}BrO$), 93 (36). MS (CI) *m/e* (rel. intensity): 287 and 285 (100, M^++H), 269 and 267 (3), 259 and 257 (3), 205 (25, M^+-Br), 177 (20), 108 (65, M^+-$C_6H_9{}^{79}BrO$), 93 (10). The purity of **3-exo** was 100% according to analysis by GC.

(1SR,3SR,4RS)-3-(3'-Bromopropyl)-1,3,4-trimethylbicyclo[2.2.2]oct-5-en-2-one (3-endo). Bromination of **11-endo** (4.9 g, 22 mmol) gave **3-endo** as a colorless oil (3.89 g, 62%) after flash chromatography. The ^1H NMR, ^{13}C NMR, IR, and HRMS spectra of **3-endo** are in good agreement with the reported values.[5b]

(1SR,3SR,4RS)-3-(3'-Bromopropyl)-1,4-Dimethylbicyclo[2.2.2]oct-5-en-2-one (13-endo). Bromination of **12-endo** (46 mg, 0.22 mmol) gave **13-endo** as a light yellow oil (51 mg, 85%) after flash chromatography. ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.24 (s, 3 H), 1.40-2.00 (9 H), 3.35 (t, J=6.8, 2 H), 5.75 (d, J=8.1, 1 H), 6.07 (d, J=8.1, 1 H). ^{13}C NMR ($CDCl_3$) δ 17.8 (q, J=127), 22.2 (q, J=126), 28.0 (t, J=125), 31.2 (t, J=130, 2 C), 34 2 (t, J=152), 35.5 (t, J=134), 40.2 (s), 49.0 (s), 52.5 (d, J=125), 131.7 (d, J=166), 140.1 (d, J=164), 214.7 (s). IR (neat) 1717 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 272 and 270 (<1, M^+), 191 (<1, M^+-^{79}Br), 162 (3), 108 (100, M^+-$C_5H_7{}^{79}BrO$), 93 (46). MS (CI) *m/e* (rel. intensity) 273 and 271(100, M^++H), 191 (28, M^+-^{79}Br), 163 (18), 108 (78, M^+-$C_5H_7{}^{79}BrO$), 93 (12). The purity of **13-endo** was >95% according to analysis by ^1H NMR.

General procedures for the preparation of bicyclo[4.2.0]oct-2-en-8-ones. (1RS,6SR,7RS)-7-(3'-Bromopropyl)-3,6,7-trimethylbicyclo[4.2.0]oct-2-en-8-one (17-exo). A solution of **3-endo** (682 mg, 2.4 mmol) in ether (15 mL) was irradiated in a pyrex vessel placed in a photochemical reactor (Rayonet, Southern New England Ultraviolet Co.) using RPR 300-nm lamps for 43 h (checking by GC for extent of completion). The solvent was evaporated. Flash chromatography (30:1 hexanes-ether) of the crude product gave **17-exo** as a clear colorless oil (457 mg, 67%). ^1H NMR ($CDCl_3$) δ 1.01 (s, 3 H), 1.22 (s, 3 H), 1.71 (s, 3 H), 1.40-2.10 (8 H), 3.42 (m, 2 H), 3.56 (br s, 1 H), 5.37 (br s, 1 H). ^{13}C NMR ($CDCl_3$) δ 13.4 (q, J=126), 18.0 (q, J=125), 23.7 (q, J=123), 26.8 (t, J=123), 28.7 t, J=146), 31.0 (t, J=129), 33.5 (s), 34.1 (t, J=151), 34.3 (t, J=110), 62.1 (d, J=134), 64.2 (s), 114.5 (d, J=158), 137.7 (s), 213.2 (s). IR (neat) 1767 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 284 and 286 (0, M^+), 135 (11), 108 (100, M^+-$C_6H_9{}^{79}BrO$), 77 (10). HRMS calcd for $C_{14}H_{21}O$ (M^+-^{79}Br): 205.1592. Found:

205.1592. The purity of **17-exo** was 100% according to analysis by GC.

(1RS,6RS,7SR)-7-(3'-Bromopropyl)-3,6-dimethylbicyclo[4.2.0]oct-2-en-8-one (18-exo). Irradiation of **13-endo** (180 mg, 0.87 mmol) gave **18-exo** a clear colorless oil (97 mg, 54%) after flash chromatography. ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.40-2.15 (8 H), 1.74 (s, 3 H), 2.97 (td, J=7.6 and 2.1, 1 H), 3.08 (br s, 1H), 3.42 (m, 2 H), 5.33 (br s, 1 H). ^{13}C NMR ($CDCl_3$) δ 22.7 (q, J=128), 23.4, 24.1, 26.8, 29.5, 30.9, 31.3, 33.5 (t, J=165), 59.5 (d, J=128), 64.4 (d, J=136), 114.8 (d, J=166), 136.1 (s), 209.2 (s). IR (neat) 1771 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 272 and 270 (0, M^+), 121 (4), 108 (100, M^+-$C_5H_7{}^{79}BrO$), 93 (69). The purity of **18-exo** was >98% according to analysis by ^{1}H NMR.

Free Radical Reaction of 3-exo. A solution of Bu_3SnH (26.8 μL, 0.10 mmol) and AIBN (2 mg) in benzene (3 mL) was added over 5 h to a stirring, refluxing solution of **3-exo** (17.0 mg, 0.06 mmol) in benzene (4 mL). Flash chromatography (20:1 hexanes-ether) of the crude product after DBU workup[13] afforded **14-exo** (9.5 mg, 77%) as a clear colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=7.1, 3 H), 1.03 (s, 3 H), 1.18 (s, 3 H), 1.20 (s, 3 H), 1.10-1.95 (8 H), 5.72 (d, J=8.0, 1 H), 6.14 (d, J=8.0, 1 H). ^{13}C NMR ($CDCl_3$) δ 15.1 (q, J=125), 17.8 (q, J=127), 18.2 (t, J=128), 19.5 (q, J=125), 22 0 (q, J=128), 30.0 (t, J=131), 30.7 (t, J=131), 36.8 (t, J=129), 43.8 (s), 48.4 (s), 49.0 (s), 130.9 (d, J=168), 144.6 (d, J=163), 216.3 (s). IR (neat) 1714 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity): 206 (3, M^+), 164 (11), 135 (10), 108 (100, M^+-$C_6H_{10}O$), 93 (27), 77 (6). HRMS calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1680. The purity of **14-exo** was >95% according to analysis by ^{1}H NMR.

Free Radical Reaction of 3-endo. A solution of **3-endo** (26.8 mg, 0.094 mmol), Bu_3SnH (32.8 μL, 0.12 mmol) and AIBN (3 mg) in benzene (24 mL) was heated for 3 h at reflux. Flash chromatography (10:1 hexanes-ether) of the crude product after DBU workup gave **15** (16.4 mg, 85%) as a clear colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3 H), 0.93 (s, 3 H), 0.95 (s, 3 H), 1.17-1.30 (m, 4 H), 1.30-1.48 (m, 4 H), 1.48-1.96 (5 H). IR (neat) 1715 (vs, C=O) cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 18.5(q, J=124), 20.1 (q, J=124), 20.1 (t, J=125), 20.7 (q, J=124), 28.0 (t, J=127), 31.1 (t, J=126), 31.6 (t, J=125), 32.9 (t, J=126), 36.6 (s), 36.7 (t, J=129), 37.9 (d, J=132), 43.2(s), 49.4 (s), 224.1 (s). MS *m/e* (rel. intensity) 206 (85, M^+), 188 (12), 173 (17), 163 (23), 132 (100), 122 (31), 107 (69), 93 (46), 81 (65), 67 (62). HRMS calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1702. The purity of **15** was >96% according to analysis by ^{1}H NMR.

Free radical Reaction of 13-endo. A solution of Bu_3SnH (19.8 μL, 0.074 mmol) and AIBN (2 mg) in benzene (3 mL) was added over 5.6 h to a stirring, refluxing solution of **13-endo** (11.4 mg, 0.042 mmol) in benzene (3 mL). Flash chromatography (40:1 hexanes-ether) of the crude product after DBU workup afforded **16** as a colorless oil (7.0 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3 H), 1.00 (s, 3 H) 1.20-1.95 (14 H). ^{13}C NMR ($CDCl_3$) δ 16.7, 20.3, 23.0, 24 3, 27.9, 29.8, 32.2, 34.1, 35.6, 37.3, 52.0, 222.0. IR (neat) 1711 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 192 (100, M^+), 174 (25), 159 (67), 145 (33), 132 (35), 119 (63), 107 (92), 93 (57). HRMS calcd for $C_{13}H_{20}O$: 192.1514. Found: 192.1511. The purity of **16** was 100% according to analysis by GC.

Free Radical Reaction of 17-exo. A solution of Bu_3SnH (0.33 mL, 1.2 mmol) and AIBN (10 mg) in benzene (10 mL) was added over 9 h to a refluxing solution of **17-exo** (151 mg, 0.53 mmol) in benzene (60 mL). GC of the reaction mixture showed **19** (2 diastereomers), **20**, and **21-exo** in the ratio of 80:11:9. Flash chromatography (40:1 hexanes-ether) of the crude product after DBU workup afforded the fast moving diastereomer of **19** (13.8 mg, 13%), the slow moving diastereomer of **19** (61.4 mg, 56%), **20** (8.2 mg, 8%), and **21-exo** (7.2 mg, 7%).

Data for the fast moving diastereomer of **19**: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J=6.8, 3 H), 0.96 (s, 3 H), 1.27 (m, 1 H), 1.40-1.90 (6 H), 1.70 (s, 3 H), 1.98 (m, 2 H), 2.30 (m, 1 H), 2.69 (m, 1 H), 2.81 (br s,

1 H), 5.13 (br.s, 1 H). ^{13}C NMR ($CDCl_3$) δ 18.2 , 23.8, 24.3 , 25.3, 27.3, 27.3, 31.4, 34.0, 41.1, 42.3, 21.4, 119.3, 136.7, 214.1. IR (neat) 1701 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 206 (23, M^+), 191 (17), 163 (19), 148 (8, M^+-C_4H_{10}), 135 (53), 126 (89), 107 (100), 93 (91), 81 (57). HRMS calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1671. The purity of fast moving diastereomer of **19** was 100% according to analysis by GC.

Data for the slow moving diastereomer of **19**: ^1H NMR ($CDCl_3$) δ 0.85 (s, 3 H), 0.87 (d, J=8.9, 3 H), 1.24-1.80 (6 H), 1.72 (s, 3 H), 1.85-2.05 (m, 3 H), 2.46 (t, J=6.6, 2 H), 3.22 (br s, 1 H), 5.10 (br s, 1 H). ^{13}C NMR ($CDCl_3$) δ 17.1 (q, J=123), 18.6 (q, J=124), 23.3 (t, J=130), 23.5 (q, J=125), 27.3 (t, J=123), 30.1 (t, J=127), 30.9 (t, J=127), 36.0 (s), 40.8 (d, J=120), 43.3 (t, J=126), 57.4 (d, J=126), 117.7 (d, J=156), 136.3 (s), 214 6 (s). IR (neat) 1700 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 206 (67, M^+), 191 (43), 163 (31), 148 (23), 135 (55), 126 (100), 107 (96), 93 (76), 81 (57). HRMS calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1671. The purity of slow moving diastereomer of **19** was 100% according to analysis by GC.

The ^1H NMR, IR, and MS spectra of **20** are identical with the literature values.[5b]

Data for **21-exo**: ^1H NMR ($CDCl_3$) δ 0.91 (t, J=7.3, 3 H), 0.99 (s, 3 H), 1.18 (s, 3 H), 1.15-2.10 (8 H), 1.70 (s, 3 H), 3.35 (br s, 1 H), 5.38 (br s, 1 H). IR (neat) 1770 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 206 (3, M^+), 188 (2), 162 (3), 135 (16), 108 (100, M^+-$C_6H_{10}O$), 93 (66), 77 (15). The purity of **21-exo** was 100% according to analysis by GC.

Free Radical Reaction of 18-exo. A solution of Bu_3SnH (47.2 μL, 0.13 mmol) and AIBN (4 mg) in benzene (5 mL) was added during 5.6 h to a refluxing solution of **18-exo** (28.6 mg, 0.11 mmol) in benzene (8 mL). GC analysis of the reaction mixture showed **36** and **37-exo** in the ratio of 62:38. Flash chromatography (40:1 hexanes-ether) of the crude product after DBU workup afforded **36** (11.2 mg, 53%) and **37-exo** (7.4 mg, 35%).

Data for **36**: ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.12-2.10 (10 H), 1.73 (s, 3 H), 2.44 (t, J=6.0, 2 H), 3.15 (br s, 1 H), 5,12 (br s, 1 H). ^{13}C NMR ($CDCl_3$) δ 21.9, 23.7, 24.2, 25.0, 27.2, 32.7, 33.4, 40.1, 42.9, 56.7, 117.6, 136.5, 214.2. IR (neat) 1701 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 192 (28, M^+), 177 (12), 159 (8), 149 (44), 134 (12), 121 (28), 112 (73), 107 (100), 93 (75), 81 (43). HRMS calcd for $C_{13}H_{20}O$: 192.1514. Found: 192.1511. The purity of **36** was 100% according to analysis by GC.

Data for **37-exo**: ^1H NMR ($CDCl_3$) δ 0.90 (t, J=7.2, 3 H), 1.12 (s, 3 H), 1.15-1.80 (6 H), 1.74 (s, 3 H), 2.11 (br s, 2 H), 2.98 (br t, J=7.0, 1 H), 3.07 (br s, 1 H), 5.34 (br s, 1 H). IR (neat) 1771 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 192 (0, M^+), 180 (1), 164 (1), 149 (3), 135 (3), 121 (10), 108 (100, M^+-C_5H_8O), 93 (100, M^+-$C_6H_{11}O$), 91 (56), 77(44). The purity of **37-exo** was >97% according to analysis by GC.

(3SR)-3-(3'-Bromopropyl)-1,3,4-trimethylbicyclo[2.2.2]octan-2-one (27). A mixture of **3-endo** (220 mg, 0.77 mmol) and 10% Pd/C (15 mg) in EtOH (6 mL) was stirred under a hydrogen balloon at room temperature for 2.5 h. The catalyst was removed by filtration. The filtrate was concentrated to give **27** as a colorless oil (185 mg, purity: >98% by GC, yield: 84%). ^1H NMR ($CDCl_3$) δ 0.84 (s, 3 H), 0.89 (s, 3 H), 1.01 (s, 3 H), 1.3-2.12 (12 H), 3.37 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ 16.5 (q, J=128), 20.7 (q, J=126), 21.5 (q, J=125), 27.8 (t, J=129), 30.1 (2 C), 30.9, 31.6, 31.9, 34.9 (t, J=151), 37.6 (s), 42.2 (s), 50.1(s), 220.8 (s). IR (neat) 1709 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 288 and 286 (0, M^+), 217 (3), 207 (100, M^+-^{79}Br), 189 (21), 163 (5), 138 (12), 119 (19), 109 (42), 95 (31), 81 (27). HRMS calcd for $C_{14}H_{23}O$ (M^+-^{79}Br): 207.1725. Found: 207.1725.

(3SR)-3-(3'-Bromopropyl)-1,4-dimethylbicyclo[2.2.2]octan-2-one (33). Hydrogenation of **13-endo** (149 mg, 0.55 mmol) using Pd/C (10 mg) as catalyst gave **33** as a colorless oil (98 mg, purity:

>98% by GC, yield: 66%). ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3 H), 0.94 (s, 3 H), 1.40-1.80 (11 H), 2.01 (m, 1 H), 2.26 (m, 1 H), 3.46 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ 20.3 (q, J=127), 24.9 (q, J=125), 25.7 (t, J=125), 28.2 (t, J=121), 30.8, 31.3, 32.0, 34.2, 35.0, 35.2 (s), 42.5 (S), 55.5 (d, J=122), 219.8 (s). IR (neat) 1714 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 274 and 272 (0, M^+), 246 (1), 193 (100, M^+-^{79}Br), 175 (18), 164 (51), 149 (45), 135 (11), 123 (11), 109 (51), 95 (52). HRMS calcd for $C_{13}H_{21}O$ (M^+-^{79}Br): 193.1592. Found: 193.1587.

(1SR,6RS,8RS)-8-(3'-Bromopropyl)-1,4,8-trimethylbicyclo[4.2.0]-7-one (23-exo). Hydrogenation of **17-exo** (140 mg, 0.50 mmol) using Pd/C (30 mg) as catalyst gave **23-exo** as a 40.5:59.5 mixture of diastereomers **A** and **B** (107 mg, 75%).

^{1}H NMR ($CDCl_3$) of the diastereomeric mixture of **23-exo**: δ 0.86 (d, J=6.6, 3 H for diastereomer **A**), 0.89 (d, J=6.5, 3 H for diastereomer **B**), 0.85-2.00 (m), 0.99 (s, 3 H for diastereomer **A**), 1.00 (s, 3 H for diastereomer **B**), 1.23 (s, 3 H for diastereomer **B**), 1.24 (s, 3 H for diastereomer **A**), 3.19 (t, J=7.8), 3.25-3.50 (m). IR (neat) 1763 (vs, C=O) cm^{-1}. MS of diastereomer **A** of **23-exo** *m/e* (rel. intensity) 288 and 286 (<1, M^+), 273 and 271 (15, M^+-CH_3), 259 and 257 (9, M^+-C_2H_5), 245 and 243 (17, M^+-C_3H_7), 207 (8, M^+-^{79}Br), 178 and 176 (62), 165 (65), 121 (17), 109 (23), 95 (58), 81 (38), 69 (100). MS for diastereomer **B** of **23-exo** *m/e* (rel. intensity): 288 and 286 (2, M^+), 273 and 271 (13, M^+-CH_3), 259 and 257 (10, M^+-C_2H_5), 245 and 243 (11, M^+-C_3H_7), 207 (12), 178 and 176 (60), 165 (61), 121 (19), 109 (19), 95 (52), 81 (28), 69 (100).

(1SR,6RS,8RS)-8-(3'-Bromopropyl)-1,4-dimethylbicyclo[4.2.0]octan-7-one (38-exo). Hydrogenation of **18-exo** (105 mg, 0.39 mmol) using PtO_2 (10 mg) as catalyst gave **38-exo** as the single diastereomer (75 mg, purity: >97% by GC, yield: 71%). ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J=6.4, 3 H), 1.60-2.10 (11 H), 1.07 (s, 3 H), 2.56 (td, J=10.0 and 1.9, 1 H), 3.3 (td, J=5.0 and 1.9, 1 H), 3.14 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ 22.3 (q, J=125), 23.1 (t, J=127), 24.6 (q, J=125), 29.2, 30.0, 30.2, 31.1, 31.5, 33.1, 33.5, 59.0 (d, J=118), 60.7 (d, J=128), 211.3 (s). IR (neat) 1765 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 274 and 272 (1, M^+), 259 and 257 (1, M^+-CH_3), 151 (5), 110 (100), 95 (85), 81 (29), 68 (38). HRMS calcd for $C_{13}H_{21}{}^{79}BrO$: 272.0776. Found: 272.0791.

Free Radical Reaction of 27. A solution of Bu_3SnH (258 µL, 0.96 mmol) and AIBN (10 mg) in benzene (15 mL) was added over 5.4 h to a stirring, refluxing solution of **27** (170 mg, 0.59 mmol) in benzene (45 mL). GC analysis of the reaction mixture showed **25**, **28**, and **29** in the ratio of 53:24:11. Flash chromatography (40:1 hexanes-ether) of the crude product after DBU workup afforded **25** (50 mg, 41%), **28** (22 mg, 18%), and **29** (7.8 mg, 8%).

Data for **25** (single diastereomer): ^{1}H NMR ($CDCl_3$) δ 0.85 (d, J=6.2, 3 H), 0.80-1.30 (5 H), 0.92 (s, 3 H), 1.01 (s, 3 H), 1.46 (m, 2 H), 1.57 (m, 2 H), 1.69 (m, 2 H), 1.88 (m, 1 H), 2.09 (m, 2 H), 2.26 (m, 1 H). ^{13}C NMR ($CDCl_3$) δ 17.4 (q, J=125), 18.0 (q, J=126), 18.7 (t, J=115), 22.6 (q, J=124), 30.5, 30.7, 30.9, 32.2, 32.6 (t, J=109), 33.6 (t, J=115), 37.4 (s), 41.2 (t, J=126), 54.1 (s), 224.3 (s). IR (neat) 1730 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 208 (<1, M^+), 137 (1), 111 (15), 98 (100), 83 (12), 69 (38). HRMS calcd for $C_{11}H_{18}O$ (M^+-C_3H_6): 166.1358. Found: 166.1358. The purity of **25** (single diastereomer) was >96% according to analysis by ^{1}H NMR.

Data for **28**: ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3 H), 0.85 (t, 3 H), 0.90 (s, 3 H), 1.01 (s, 3 H), 1.35-1.90 (12 H). ^{13}C NMR ($CDCl_3$) δ 12.5, 16.6, 18.0, 21.0, 21.8, 30.4 (2 C), 31.2, 32.1, 36.1, 37.8, 42.5, 51.1, 221.7. IR (neat) 1711 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 208 (4, M^+), 190 (2), 166 (38), 138 (100), 126 (8), 109 (15), 95 (14), 81 (12), 69 (20). HRMS calcd for $C_{14}H_{24}O$: 208.1827. Found: 208.1827. The purity of **28** was >95% according to analysis by ^{1}H NMR.

The IR, MS spectra, and GC retention time of **29** agree well with those of an authentic

sample.

Preparation of an Authentic Sample of 29. Hydrogenation of (1SR,3SR,4RS)-1,4-dimethyl-3-methylbicyclo[2.2.2]oct-5-en-2-one (55.1 mg, 0.34 mmol) using Pd/C (5 mg) as catalyst gave **29** as a colorless oil (50.4 mg, purity: >98%, yield: 89%). ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 3 H), 0.90 (s, 3 H), 1.05 (d, J=7.3, 3 H), 1.30-1.70 (8 H), 1.90 (q, J=7.4, 1 H). ^{13}C NMR ($CDCl_3$) δ 10.9 (q, J=127), 20.4 (q, J=126), 24.8 (q, J=125), 27.5 (t, J=110), 27.6 (s), 30.5 (t, J=126), 31.7 (t, J=127), 34.7 (t, J=128), 42.0 (s), 51.5 (d, J=124), 220.6 (s). IR (neat) 1716 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 166 (13, M^+), 151(1, M^+-CH_3), 137 (1, M^+-C_2H_5), 123 (2, M^+-C_3H_7), 108 (100, M^+-C_3H_4O), 93 (25, M^+-C_4H_7O), 81 (10, M^+-$C_5H_{10}O$). HRMS calcd for $C_{11}H_{18}O$: 166.1359. Found: 166.1359. The purity of **29** was 100% according to analysis by GC.

Free Radical Reaction of 33. A solution of Bu_3SnH (61 μL, 0.23 mmol) and AIBN (5 mg) in benzene (8 mL) was added over 5.6 h to a stirring, refluxing solution of **33** (35 mg, 0.13 mmol) in benzene (10 mL). GC analysis of the reaction mixture showed **34** as a single diastereomer and **35** in the ratio of 53:47. Flash chromatography (40:1 hexanes-ether) of the crude product after DBU workup afforded **34** (10.6 mg, 42%), **35** (8.8 mg, 35%).

Data for **34** (single diastereomer): ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J=6.4, 3 H), 0.92 (s, 3 H), 1.11 (m, 2 H), 1.15-2.15 (13 H), 2.26 (m, 1 H). ^{13}C NMR ($CDCl_3$) δ 18.9, 20.4, 22.6, 25.6, 30.3, 30.5, 32.6, 35.1, 35.2, 35.7, 40.9, 59.7, 220.9. IR (neat) 1732 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 194 (1, M^+), 110 (17), 95 (18), 84 (100), 69 (19). The purity of **34** was >95% according to analysis by GC.

Data for **35**: ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3 H), 0.92 (s, 3 H), 0.92 (t, J=6.8, 3 H), 1.40-1.80 (13 H). ^{13}C NMR ($CDCl_3$) δ 14.4, 20.4, 22.8, 25.0, 28.3, 29.6, 31.0, 31.3, 35.1, 35.2, 42.5, 56.7, 220.4. IR (neat) 1715 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 194 (5, M^+), 152 (30), 137 (3), 124 (100), 108 (29), 93 (18), 81 (15). HRMS calcd for $C_{13}H_{22}O$: 194.1671. Found: 194.1657. The purity of **35** was >95% according to analysis by GC.

Free Radical Reaction of 23-exo (mixture of two diastereomers). A solution of Bu_3SnH (151 μL, 0.56 mmol) and AIBN (10 mg) in benzene (11 mL) was added over 6 h to a stirring, refluxing solution of **23-exo** (107 mg, 0.37 mmol) in benzene (25 mL). GC analysis of the reaction mixture showed **24** (four diastereomers: **A**, **B**, **C**, and **D**), **25** (two diastereomers: **A** and **B**), and **26-exo** (two diastereomers: **A** and **B**) in the ratio of 68 (11:6:24:27) : 22 (9:13) : 10 (7:3). Flash chromatography (45:1 hexanes-ether) of the crude product after DBU workup afforded diastereomer **D** of **24** (15.3 mg, 20%), diastereomer **C** of **24** (18.4 mg, 24%), a mixture of diastereomers **A** and **B** of **24** (10.2 mg, 13%), a mixture of diastereomers **A** and **B** of **25** (11.6 mg, 15%), and a mixture of diastereomers **A** and **B** of **26-exo** (6.2 mg, 8%).

Data for diastereomer **D** of **24**: ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3 H), 0.85 (d, J=6.9, 3 H), 0.95 (d, J=6.1, 3 H), 0.80-1.90 (11 H), 2.20 (m, 1 H), 2.36 (m, 2 H), 2.59 (m, 1 H). ^{13}C NMR ($CDCl_3$) δ 17.9, 21.9, 22.4, 22.6, 29.6, 29.8, 33.0 (2 C), 33.5, 34.5, 38.9, 42.1, 66.5, 216.6. IR (neat) 1684 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 208 (18, M^+), 193 (9, M^+-CH_3), 165 (9), 137 (24), 126 (26), 110 (53), 95 (100), 81 (67). HRMS calcd for $C_{14}H_{24}O$: 208.1827. Found: 208.1774. The purity of diastereomer **D** of **24** was 100% according to analysis by GC.

IR (neat) of the mixture of diastereomers **A** and **B** of **25**: 1732 (vs, C=O) cm^{-1}. MS of diastereomers **A** of **25***m/e* (rel. intensity): 208 (<1, M^+), 137 (2), 111 (37), 98 (100), 83 (37), 69 (53).

IR (neat) of the mixture of diastereomers **A** and **B** of **26-exo**: 1763 (vs, C=O) cm^{-1}. MS of diastereomer **A** of **26-exo** *m/e* (rel. intensity): 208 (11, M^+), 193(4, M^+-CH_3), 179 (12), 166 (29), 137 (53), 109 (30), 98 (49), 81 (26), 69 (100).

Free Radical Reaction of 38-exo. A solution of Bu_3SnH (63 μL, 0.2 mmol) and AIBN (5 mg) in benzene (5 mL) was added over 8 h to a stirring, refluxing solution of **38-exo** (30 mg, 0.1 mmol) in benzene (10 mL). GC of the reaction mixture showed **39**, **34** (single diastereomer), and **40-exo** in the ratio of 49:14:37. Flash chromatography (40:1 hexanes-ether) of the crude product after DBU workup afforded **39** (8.1 mg, 42%) and a mixture of **34** and **40-exo** (7.9 mg).

Data for **39**: ^1H NMR ($CDCl_3$) δ 0.94 (s, 3 H), 0.95 (d, J=5.7, 3 H), 1.20-1.80 (12 H), 2.15 (br t, J=14.1, 1 H), 2.26-2.22 (2 H), 2.62 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 22.5, 23.5, 24.4, 27.9, 29.8, 30.2, 32.9, 33.5, 35.9, 42.4, 43.0, 64.5, 216.2. IR (neat) 1688 (vs, C=O) cm^{-1}. MS *m/e* (rel. intensity) 194 (10, M^+), 179(13, M^+-CH_3), 161(7), 137 (17), 112 (100), 95 (44), 81 (73), 67 (56). HRMS calcd for $C_{13}H_{22}O$: 194.1671. Found: 194.1671. The purity of **39** was 100% according to analysis by GC.

IR (neat) of the mixture of **34** and **40-exo**: 1771 (vs, C=O for **40-exo**), 1732 (vs, C=O for **34**) cm^{-1}. MS of **34** *m/e* (rel. intensity): 194 (<1, M^+), 110 (21), 95, (16), 84 (100), 69 (16). MS of **40-exo** *m/e* (rel. intensity): 194 (5, M^+), 151 (4), 137 (3), 123 (5), 110 (71), 95 (100), 81 (31), 68 (62).

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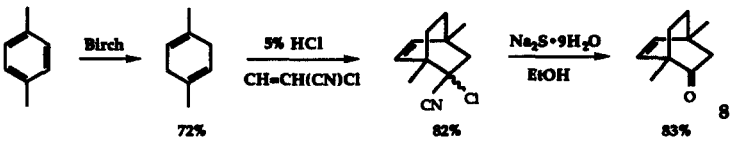

(i)

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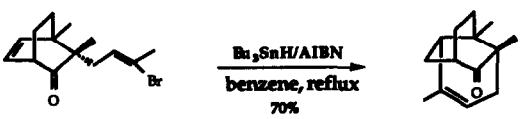

(ii)

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