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Ring Scission of Diastereomeric 4-Butylspiropentylcarbinyl Radicals as a Chemical Model for Identifying Enzyme-Catalyzed FAD Adducts Resulting from Spiropentylacetyl-CoA

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Abstract: Both diastereomeric 4-butylspiropentylcarbinyl bromides (**14a** and **14b**) were synthesized in seven steps starting from 1-heptyne, and the stereochemical assignments based upon NOE experiments were confirmed by converting their immediate alcohol precursors (**13a** and **13b**) to 1,4-dibutylspiropentanes (**17a** and **17b**) with C_1 and C_2 symmetry. Each bromide was used to generate its corresponding spiropentylcarbinyl radical (**18a** and **18b**) via its AIBN-initiated tri-*n*-butyltin hydride reduction. The radical-trapped products are identified, the preferred ring scission mode is identified (C1−C2 bond cleavage), and the estimated rates for the ring opening of 4-butylspiropentylcarbinyl radical (**18**, k_{25} °C $\geq \sim 5 \times 10^9$ s^{-1}) and 2-butyl-1-vinylcyclopropylcarbinyl radical (**33**, k_{25} °C $\sim 5 \times 10^8$ s^{-1}) are reported. High-level ab initio calculations addressing the ring-opening isomerizations of cyclopropylcarbinyl and spiropentylcarbinyl radicals also are presented. These results in conjunction with a previous study enable us to propose two structures for the enzyme-catalyzed FAD adducts resulting from spiropentylacetic acid-CoA, a synthetic byproduct of fatty acid metabolism.

Introduction

An important class of enzymes involved in fatty acid metabolism is the FAD-dependent acyl-CoA dehydrogenases.[1] A wide variety of inhibitors have been reported for these enzymes.[2−6] One such inhibitor is (methylenecyclopropyl)acetyl-CoA (MCPA-CoA), a metabolite of hypoglycin A,[2] which inactivates both medium-chain (MCAD) and short-chain (SCAD) acyl-CoA dehydrogenases via covalent modification of FAD. Both enantiomers of MCPA-CoA have been shown to be effective inhibitors[3a,b,d] and the lack of stereospecificity in the ring scission has been taken as evidence for the intermediacy of a cyclopropylcarbinyl radical.[3] Tserng et al. have shown that the more highly strained compound, spiropentylacetic acid (SPA), a synthetic byproduct of fatty acid metabolism, inhibits MCAD without affecting amino acid metabolism. This led them to the conclusion that SPA-CoA is a tight-binding inhibitor.[5] More recently, the inhibitory properties of SPA-CoA (**1**) were reexamined against two acyl-CoA dehydrogenases: *pig liver* MCAD and a recombinant *Mega-sphaera elsdenii* SCAD.[6] In contrast to the earlier conclusion,[5] SPA-CoA was found to be an irreversible mechanism-based inactivator for these enzymes. The formation of a covalent linkage between SPA-CoA and the FAD cofactor of MCAD and SCAD was revealed using tritium-labeled SPA-CoA. More importantly, both (*R*)- and (*S*)-SPA-CoA could effectively inactivate MCAD, and the resulting inhibitor-FAD adducts appeared to have one of the three-membered rings of the spiropentyl moiety cleaved. Since the inactivation is nonstereospecific with respect to C_β bond scission, the ring opening of SPA-CoA leading to enzyme inactivation is likely initiated by a spiropentylcarbinyl radical (**3**).[6] As depicted in Scheme 1, radical-induced cleavage of the spiro-

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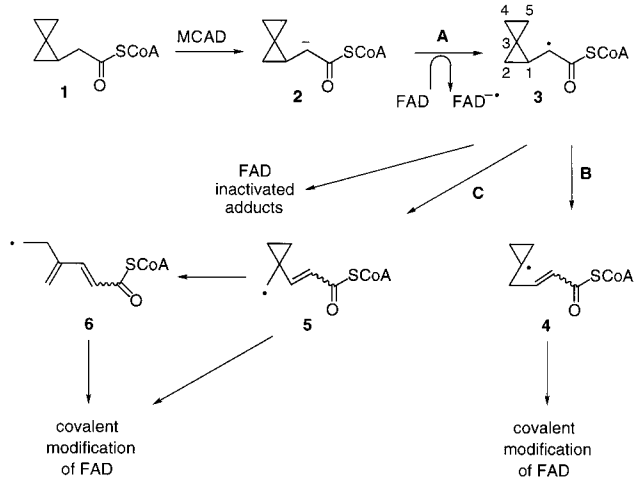
Scheme 1



pentyl system could generate either a tertiary cyclopropyl (**4**) or a primary cyclopropylcarbinyl radical (**5**). Subsequent ring opening of **5** could afford an acyclic radical intermediate (**6**). NMR analysis using ^{13}C-labeled SPA-CoAs as probes had ruled out the participation of **6** in FAD-adduct formation; however, whether **4** or **5** is the reactive intermediate responsible for FAD modification could not be unambiguously determined. In this report, we describe a chemical model study of the ring scission of diastereomeric spiropentylcarbinyl radicals and propose two structures for the identity of the enzyme-catalyzed FAD adducts resulting from SPA-CoA. High-level ab initio calculations on the ring opening of spiropentylcarbinyl radical also are described.

Results and Discussion

Preparation of Spiropentylcarbinyl Bromides (14a and 14b). (*E*)- and (*Z*)-4-Butyl-1-bromomethylspiropentane (**14a** and **14b**) were employed as spiropentylcarbinyl radical precursors. The *n*-butyl substituent at C4 was incorporated into the substrate to make the radical decomposition products less volatile and to provide a means for determining the influence of a remote stereocenter on the composition of the ring-opened products. Both bromides were synthesized via a seven-step sequence starting with 1-heptyne (**7**, Scheme 2). Reaction of the lithium acetylide of **7** with paraformaldehyde afforded 2-octyn-1-ol (**8**) which was converted to (*Z*)-3-iodo-2-octen-1-ol (**9**), along with a small amount of the regioisomer **10**, upon treatment with Red-Al and iodine. Cyclopropanation of **9** with Charette's reagent (a modified Simmons−Smith reaction)[7] led to the formation of cyclopropylmethyl alcohol **11**. Dehydroiodination of this compound gave a 1:1 mixture of homoallylic alcohols **12a** and **12b**. These two isomers were separated by chromatography and subsequent reactions were carried out using each individually. Their stereochemical assignment was based upon the NOE (PFT NOE) experiments[8] discussed below. Cyclopropanation of the exocyclic double bonds proceeded stereospecifically to yield spiropentane derivatives **13a** and **13b**, respectively. These alcohols were then converted to their corresponding bromides (**14a** and **14b**) by using triphenylphosphine and carbon tetrabromide. These bromides served as the free radical precursors required for studying the regioselectivity of radical-induced ring opening.

Structural Analysis and Assignment of Configuration. Nuclear Overhauser experiments were carried out to determine the relative stereochemistry of 2-pentylidene-1-hydroxymethylcyclopropanes **12a** and **12b**.[8] Compound **12a** was assigned the *anti* configuration on the basis of the observed NOE interaction between the olefin proton (δ 5.85) and the methylene protons of the hydroxymethyl substituent (δ 3.48 and 3.58). In isomer **12b**, the allylic protons (δ 2.16) of the pentylidene substituent interact with methylene protons of the hydroxymethyl group (δ 3.40 and 3.73) and the vinyl proton (δ 5.80) interacts with the cyclopropyl methylene protons (δ 0.92 and 1.28), thereby allowing the assignment of the *syn* configuration.

Cyclopropanation of homoallylic alcohols **12a** and **12b** proceeds stereoselectively with retention of configuration to yield **13a** and **13b**, respectively. The observed selectivity can be rationalized by the directing effect of the hydroxyl group, a common feature of cyclopropanation of allylic alcohols, as has been reported in several instances for homoallylic species.[9] An approach first described by Gajewski and Burka[10] was used to verify the stereochemical assignments of these substituted spiropentanes (**13a** and **13b**). In principle, as shown in Scheme 3, cyclopropanation of (*E*)-*anti* isomer **12a** could give spiropentanes **13a** and **13c** while (*Z*)-*syn* isomer **12b** could give spiropentanes **13b** and **13d**. The terms *proximal*, *medial*, and *distal*[10] refer to the relative distances on a line between the substituents in the four possible isomers (**13a**−**13d**). Both *medial* compounds can be further differentiated by the terms *syn* and *anti* which refer to the relative positions of the substituents using the plane of the three-membered ring bearing the higher priority substituent as a plane of reference.

As illustrated in Scheme 3, if the hydroxymethyl group directs the cyclopropanation so that the addition of methylene comes in *syn* to it, the *distal* isomer **13a** will result from (*E*)-*anti* isomer **12a** and the *medial*-*anti* isomer **13b** will arise from (*Z*)-*syn* isomer **12b**. If the methylene group were to come in *anti* to the hydroxymethyl substituent, then the *medial*-*syn* isomer **13c** and the *proximal* isomer **13d** would result from **12a** and **12b**, respectively. To identify the stereochemistry of the isolated products, the hydroxymethyl groups were converted to butyl groups so as to have equivalent substituents on the spiropentyl moiety (Scheme 4). In the *distal* and *proximal* alcohols (**13a** and **13d**, respectively), these compounds would lead to the formation of 1,4-dibutyl derivatives with C_2 symmetry and would therefore have only one set of signals in the ^{1}H and ^{13}C NMR spectra. Both *medial* compounds (**13b** and **13c**) would afford 1,4-dibutyl derivatives with C_1 symmetry and would have two sets of resonances in the NMR spectra.

Alcohols **13a** and **13b** were converted to the corresponding aldehydes **15a** and **15b** via a tetrapropylammonium perruthenate (TPAP)/4-methylmorpholine *N*-oxide (*N*-MMO) oxidation. Further reactions were carried out on the crude aldehydes as they decomposed upon purification. Wittig olefination of **15a** and

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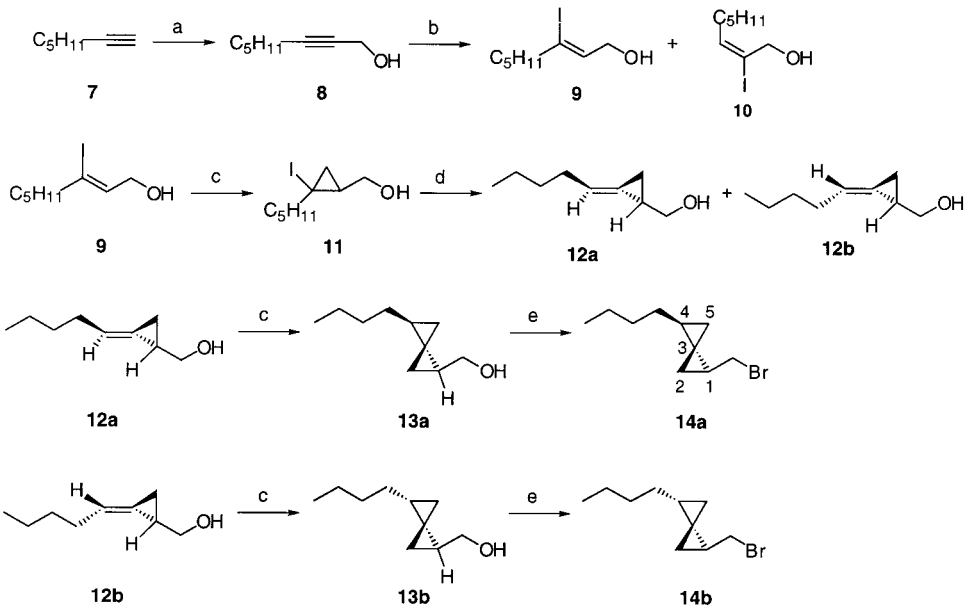
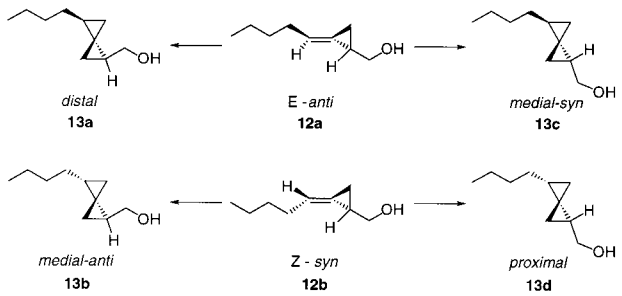
Scheme 2[a]



[a] Conditions: (a) *n*-BuLi, $(CH_2O)_n$, THF (90%); (b) Red-Al, EtOAc, I_2/THF (76%); (c) $ZnEt_2$, CH_2I_2, $TiCl_4$, CH_2Cl_2 (57−78%); (d) *t*-BuOK, DMSO (74%); (e) Ph_3P, CBr_4 (99%).

Scheme 3



15b affords **16a** and **16b**, which can be reduced with diimide to give the desired 1,4-dibutylspiropentanes (**17a** and **17b**). The ^{1}H NMR spectrum of **17a** has one set of cyclopropyl resonances and the ^{13}C spectrum has seven lines indicating that this compound has C_2 symmetry. In contrast, **17b** displays two sets of cyclopropyl hydrogens in the ^{1}H NMR spectrum and twelve carbon resonances in the ^{13}C NMR spectrum (one set of lines is overlapping) indicating that this species has C_1 symmetry. These results indicate that cyclopropanation of the homoallylic alcohols **12a** and **12b** proceeds from the same side as the hydroxymethyl group to afford **13a** and **13b**, respectively.

Preparation of (*E*)- and (*Z*)-4-Butyl-1-methylspiropentane (19a and 19b), (*E*)- and (*Z*)-2-Butyl-1-methyl-1-vinylcyclopropane (20a and 20b), *cis*- and *trans*-1-Allyl-2-butylcyclopropane (21a and 21b), and 4-Methyl-3-methylene-1-octene (22). To facilitate the determination of the trapped products derived from both 4-butylspiropentylcarbinyl radicals (**18a** and **18b**), we independently synthesized **19**−**22** as these compounds were expected to be formed in small amounts, if at all. The first of these species was generated simply by the lithium aluminum hydride reduction of (*E*)- and (*Z*)-4-butyl-1-bromomethylspiropentane (**14a** and **14b**, Scheme 5). A 77:23 stereoisomeric mixture of the vinylcyclopropanes was prepared in a four-step sequence starting with 3,4-epoxy-3-methyl-1-butene (**23**). In particular, reaction of *n*-propylcuprate with epoxide **23** affords a 77:23 mixture of (*E*)- and (*Z*)-2-methylhept-2-en-1-ol, which can be converted to the corresponding cyclopropylcarbinyl alcohols (**25a** and **25b**) by a modified Simmons−Smith reaction.[7] Oxidation to the aldehydes (**26a** and **26b**) with *N*-MMO and TPAP followed by a Wittig olefination afforded the desired (*E*)- and (*Z*)-2-butyl-1-methyl-1-vinylcyclopropane (**20a** and **20b**). A 5:95 cis-to-trans mixture of 1-allyl-2-butylcyclopropane (**21a** and **21b**) was synthesized from 1-hexyne via a previously reported transformation to *cis*- and *trans*-1-bromo-2-butylcyclopropane (5:95)[11] and subsequent conversion to the target compound by a cuprate reaction. The final substrate (**22**) was made by 1,2-addition of the Grignard reagent derived from 2-bromohexane to acrolein followed by *N*-MMO/TPAP oxidation of the allylic alcohol (**30**) and Peterson olefination of the α,β-unsaturated ketone (**31**).

Generation and Fate of 4-Butylspiropentylcarbinyl Radicals (18a and 18b). As mentioned earlier, the mechanism of irreversible inactivation of MCAD and SCAD by SPA-CoA was recently proposed to proceed via C_α−H deprotonation followed by a one-electron oxidation of the anion intermediate **2** to give spiropentylcarbinyl radical **3** (Scheme 1).[6] Rapid isomerization of this strained moiety is expected and observed (see below) and should afford tertiary cyclopropyl radical **4** or primary cyclopropylcarbinyl radical **5**; subsequent ring opening of the latter species would give acyclic intermediate **6**. The concurrently formed one-electron-reduced flavin semiquinone could be intercepted, in principle, by any or all of these intermediate radicals leading to irreversible covalent modification of the cofactor and ultimately enzyme inactivation. On the basis of ^{13}C-labeling experiments, only single ring-opened radicals (**4** and **5**) were postulated as reactive intermediates responsible for FAD modification.[6] To distinguish between these two possibilities and to facilitate the elucidation of the FAD adducts, we decided to explore the radical-trapping products derived from both (*E*)- and (*Z*)-4-butylspiropentylcarbinyl radicals (**18a** and **18b**).

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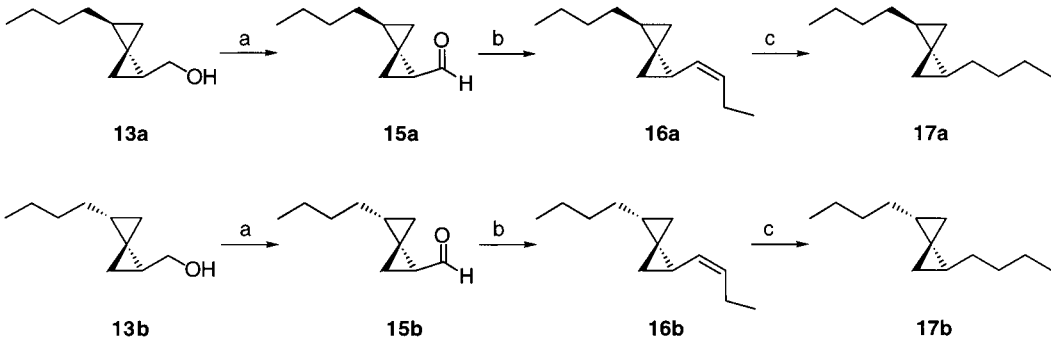
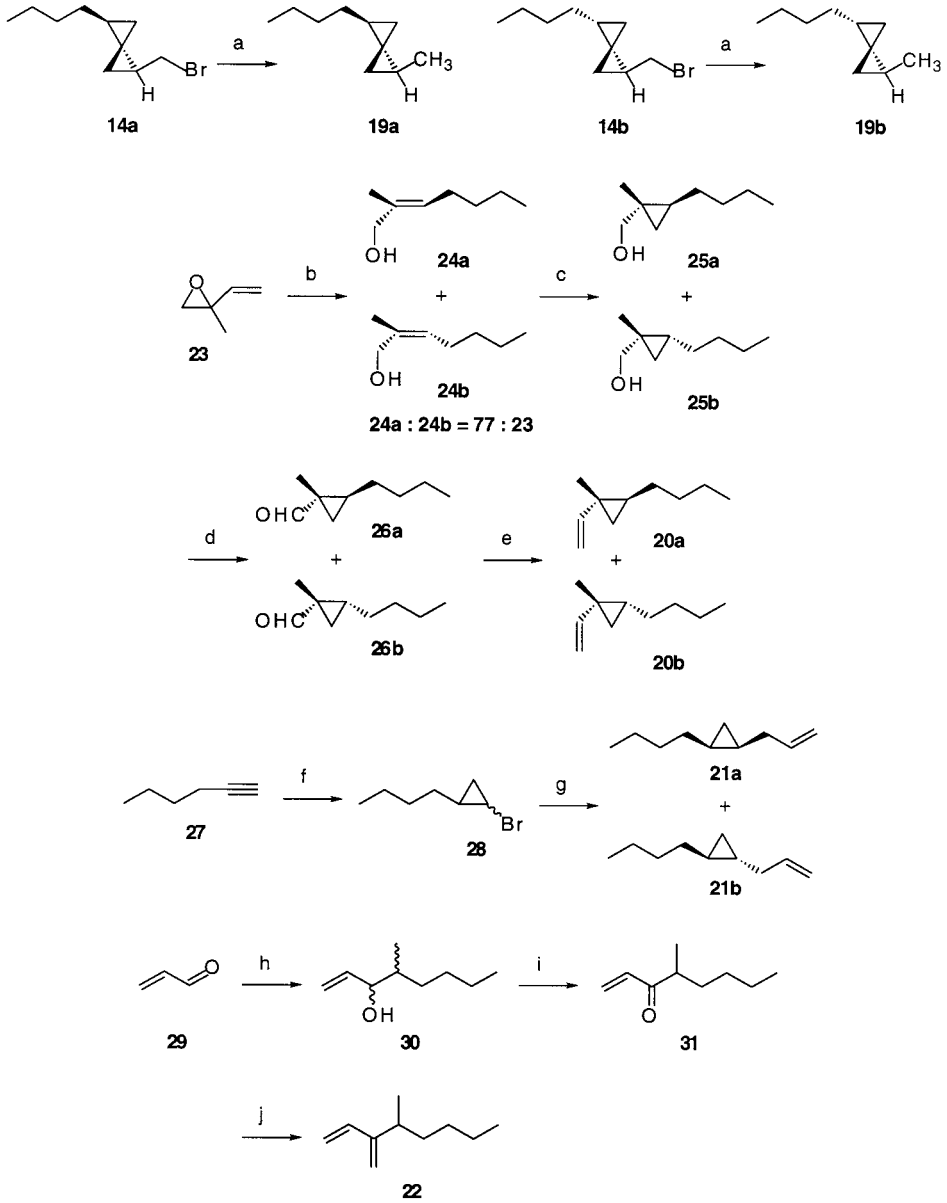
Scheme 4[a]



[a] Conditions: (a) *N*-MMO, TPAP, CH_2Cl_2; (b) $Ph_3P^+C_3H_7Br^-$, THF (84% for two steps); (c) NH═NH (82−84%).

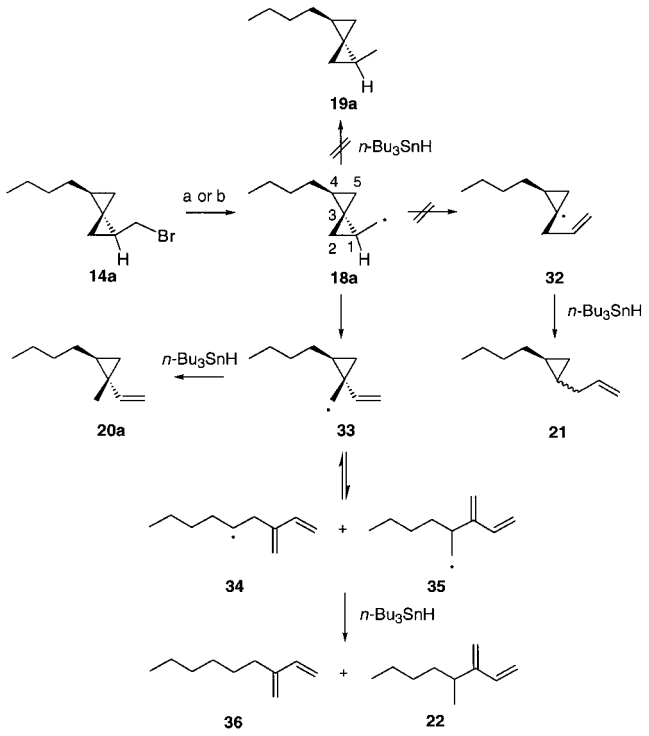
Scheme 5[a]



[a] $LiAlH_4$, Et_2O (48−50%); (b) $C_3H_7Li(Cu)$, Et_2O (84%); (c) $ZnEt_2$, CH_2Cl_2, $TiCl_4$, CH_2Cl_2 (85%); (d) *N*-MMO, TPAP, CH_2Cl_2 (96%); (e) $Ph_3P^+CH_3Br^-$, THF (59%); (f) 1. Dibal-H, 2. Zn(Cu), CH_2Br_2, 3. Br_2, H^+ (36%); (g) Bu_2CuLi, allyl bromide (46%); (h) 2-$C_6H_{13}MgBr$ (34%); (i) *N*-MMO, TPAP, CH_2Cl_2 (83%); (j) $TMSCH_2Li$, THF, AcCl (15%).

Isomerization of spiropentylcarbinyl radical **18a** can lead to tertiary cyclopropyl radical **32** and primary cyclopropylcarbinyl radical **33** depending upon which bond breaks during the ring-opening process (Scheme 6). To determine which pathway (C1−C2 or C1−C3 cleavage) is preferred and to assess the effect of a remote stereocenter on the regioselectivity of the ring cleavage, diastereomeric spiropentylcarbinyl radicals were generated by the AIBN initiated tri-*n*-butyltin hydride reduction of bromides

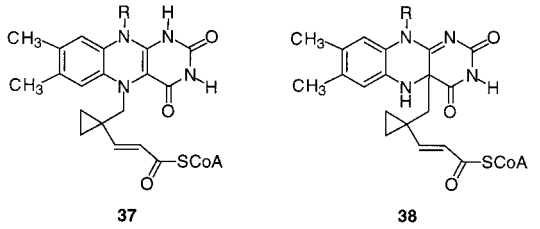
Scheme 6[a]



[a] Conditions: (a) *n*-Bu_3SnH, AIBN, PhH, 80 °C; (b) neat *n*-Bu_3SnH, AIBN, 4, 24, and 70 °C.

14a and **14b** in refluxing benzene and in the absence of a solvent at 4, 24, and 70 °C.[12−14] In each case ring-opened products, 3-methylene-1-nonene (**36**) and 4-methyl-3-methylene-1-octene (**22**), were obtained in 13:1 ratios, respectively. Identification of the two dienes was carried out after separation by preparative gas−liquid chromatography on the basis of their NMR and mass spectral data. The major isomer (**36**) has been reported previously by Katritzky et al.[15] and there is good accord between our ^1H and ^{13}C NMR spectral data and those in the literature. As for the minor isomer (**22**), it was independently synthesized and the GC-MS and ^1H NMR spectral data match those obtained from the material derived from **14a** and **14b**. No 4-butyl-1-methylspiropentane (**19**) or 1-allyl-2-butylcyclopropane (**21**) was detected in any of these experiments, but 1−2% of 2-butyl-1-methyl-1-vinylcyclopropane (**20**) was found in neat tri-*n*-butyltin hydride when we specifically looked for minor products using gas chromatography−mass spectrometry.[16]

Scheme 7



Taken together, these experiments indicate that 4-butylspiropentylcarbinyl radicals (**18a** and **18b**) undergo C1−C2 bond cleavage to afford a primary cyclopropylcarbinyl radical intermediate (e.g., **33**), as opposed to breaking the C1−C3 bond to give a tertiary cyclopropyl radical (e.g., **32**). Subsequent cleavage of **33** or its *Z*-isomer affords homoallylic radicals **34** and **35**, both of which lead to the major products upon hydrogen atom abstraction; the initial stereochemistry of the first formed radical (**18a** and **18b**) has no effect on the product distribution. In neat tri-*n*-butyltin hydride, **33** is trapped to a small extent (∼1−2%). This finding is consistent with the previously reported 9% trapping of cyclopropylcarbinyl radical under the same reaction conditions.[17] These results also indicate that **33** isomerizes ∼5 times faster than cyclopropylcarbinyl radical (i.e., k_{25} °C $\sim 5 \times 10^8$ s^{-1})[18] and **18** rearranges at least 10 times more rapidly than **33** (i.e., k_{25} °C $\geq \sim 5 \times 10^9$ s^{-1}). Both of these rate enhancements can be attributed to the effects of substituents on the ring-opening isomerization of cyclopropylcarbinyl radicals.[6,18] Last, the preference for C1−C2 bond cleavage in **18** is in accord with the 9 kcal mol^{-1} difference between the cyclopropyl and cyclopropylcarbinyl C−H bond strengths (106.3 ± 0.3[19] and 97.4 ± 1.6[20] kcal mol^{-1}, respectively), and the expectation that the additional stabilization of a tertiary cyclopropyl radical (≤3 kcal mol^{-1}) as in **32** will be effectively canceled by the conjugative interaction between the vinyl group and the cyclopropane ring in **33**.[21] On the basis of these findings and those obtained by Li et al.,[6] we propose that the major covalent FAD adducts in the enzyme-catalyzed cleavage of SPA-CoA are derived from cyclopropylcarbinyl radical **5** (Scheme 7) and those species arising from cyclopropyl radical **4** can be eliminated from further consideration.

Computations. To obtain additional insights into the ring-opening process of spiropentylcarbinyl radicals, ab initio mo-

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(16) Retention times and EI mass spectra are as follows. **20a**: 3.91 min, *m*/*z* 138 (9), 123 (3), 110 (4), 109 (15), 95 (19), 81 (60), 68 (100), 67 (75), 55 (19), 53 (21). **20b**: 3.73 min, *m*/*z* 138 (9), 123 (3), 110 (3), 109 (15), 95 (18), 81 (59), 68 (100), 67 (75), 55 (17), 53 (19). Radical rearrangement product from **14a**: 3.91 min, *m*/*z* 138 (6), 109 (15), 95 (34), 81 (73), 68 (99), 67 (100), 55 (47), 53 (26). Radical rearrangement product from **14b**: 3.72 min, *m*/*z* 138 (5), 109 (13), 95 (25), 81 (66), 68 (100), 67 (71), 55 (21), 53 (24). The minor differences in the intensities of the fragment ions can readily be attributed to the low concentration of the isomerization products.

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(21) The difference in the $(CH_3)_2CH-H$ and $(CH_3)_3C-H$ bond dissociation energies is 2.6 ± 0.7 kcal mol^{-1} (Weast, R. C. In *CRC Handbook of Chemistry and Physics*, 70th ed.; CRC Press: Boca Raton, FL, 1989) or 2.1 ± 0.6 kcal mol^{-1} (Berkowitz, J.; Ellison, G. B.; Gutman, D. *J. Phys. Chem.* **1994**, *98*, 2744). As one might expect a methyl group to have less impact on cyclopropyl radical because of reduced hyperconjugation, the additional stabilization brought about by the tertiary center in **32** should be ≤ ∼3 kcal mol^{-1} and will be approximately canceled by the conjugation energy of the vinyl group with the cyclopropane in **33**.

Scheme 8

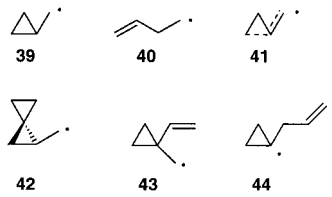

Table 1. Computed Relative Energies of Cyclopropylcarbinyl Radical (**39**), Homoallyl Radical (**40**), and the Transition State (**41**) Interconverting Them at Different Computational Levels

	relative energies (kcal mol^{-1}) at 298 K[b]		
method[a]	**39**	**40**	**41**
HF/6-31G(d)	0	−5.1	10.0
MP2/6-31G(d)//HF/6-31G(d)	0	0.6 (0.0)	14.9 (7.7)
MP2/6-31G(d)//MP2/6-31G(d)	0		16.9 (9.4)
MP2/cc-pVDZ	0	−1.8 (−2.1)	15.8 (8.6)
MP3/cc-pVDZ	0	−3.8 (−4.2)	14.6 (9.1)
MP4(SDQ)/cc-pVDZ	0	−4.4	12.9
CCSD/cc-pVDZ	0	−5.0	10.2
CCSD(T)/cc-pVDZ	0	−5.2	9.3
MP2/6-311+G(2df,2pd)	0	−0.5 (−2.9)	15.5 (8.2)
MP3/6-311+G(2df,2pd)	0	−2.8 (−4.9)	13.9 (8.4)
MP4(SDQ)/6-311+G(2df,2pd)	0	−3.4	12.3
CCSD/6-311+G(2df,2pd)	0	−3.8	9.8
CCSD(T)/6-311+G(2df,2pd)	0	−3.9	8.8
expt[c]	0	−3.1	7.1

[a] All of the calculations using the cc-pVDZ and 6-311+G(2df,2pd) basis sets were carried out on MP2/6-31G(d) (**39** and **41**) or QCISD/6-31G(d) (**40**) optimized structures. [b] Parenthetical values correspond to PMP2 or PMP3 energies. [c] See refs 18b, h, j, and 23.

lecular orbital calculations were carried out.[22] First, we explored the ring cleavage of cyclopropylcarbinyl radical since this system has been studied in detail experimentally.[17,18] Such a study will also provide a means to benchmark our computations and determine what level of theory is required to obtain reliable results. Unrestricted Hartree−Fock and MP2 or QCISD geometry optimizations were carried out with the 6-31G(d) basis set for cyclopropylcarbinyl radical (**39**), homoallyl radical (**40**), and the transition state (**41**) interconverting these two species (Scheme 8, full details including geometries and absolute energies can be found in the Supporting Information).[23] Single-point energy calculations were subsequently performed at a variety of computational levels with several different basis sets, and the energies are compared to experiment in Table 1. At the highest level of theory we explored (CCSD(T)/6-311+G(2df,-2pd)), our results reproduce the cyclopropylcarbinyl-homoallyl radical difference to within 0.8 kcal mol^{-1} (−3.9 (calc) and −3.1 (expt)[18b,24] kcal mol^{-1}) and the ring-opening barrier to within 1.7 kcal mol^{-1} (8.8 (calc) and 7.1 (expt)[18h,j] kcal mol^{-1}). Use of Dunning's smaller correlation-consistent double-ζ basis set (cc-pVDZ)[25] leads to systematically poorer results but only by 0.5 kcal mol^{-1} in the barrier height and 1.3 kcal mol^{-1} in the **39**−**40** energy difference (i.e., the discrepancy with experiment is 2.1−2.2 kcal mol^{-1} in both cases). Given the much more economical nature of this basis set, particularly when applied to the larger spiropentylcarbinyl radical system, we decided to employ it and apply an empirical correction of −2.2 kcal mol^{-1} to the computed CCSD(T) isomerization barriers.

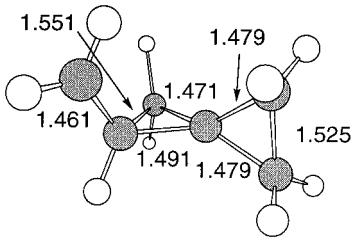

Figure 1. MP2/6-31G(d) optimized geometry of spiropentylcarbinyl radical (**42**).

Full geometry optimizations for methylspiropentane, spiropentylcarbinyl radical (**42**), 1-vinylcyclopropylcarbinyl radical (**43**), 1-allylcyclopropyl radical (**44**), and the corresponding ring-opening transition structures were carried out at the UHF and UMP2 levels with the 6-31G(d) basis set (Figure S2 in the Supporting Information). Upon removal of a hydrogen atom from methylspiropentane to afford **42**, the C1−C3 bond elongates by 0.009 Å and the C1−C2 bond stretches three times as much (0.026 Å) at the MP2 level (Figure 1). These geometry changes suggest that spiropentylcarbinyl radical is stabilized by conjugation of the radical center with the adjacent three-membered ring and that the C1−C2 bond is the weakest one in the molecule. This is consistent with G2[26] 298 K bond dissociation energies for the cyclopropylcarbinyl-H and 1-methylcyclopropyl-H bonds (99.9 and 107.6 kcal mol^{-1}, respectively)[27] and the computed relative energies of **43** (0) and **44** (+9.5 kcal mol^{-1}, Table 2). To our surprise, the spiropentylcarbinyl radical is predicted to be virtually as stable as the 1-allylcyclopropyl radical. Apparently, conjugation of the radical center in **42** is particularly effective and helps relieve some of the additional strain energy in the spiropentane ring system. As for the ring-opening barriers, the isomerization of **42** to **43** is predicted to be much more facile ($\sim 1 \times 10^4$ at 25 °C) than to **44** as shown in our experiments. The absolute barrier heights (i.e., $\Delta H^{\ddagger} = 4.0$ vs 9.6 kcal mol^{-1}, respectively) are insensitive to the computational method after correcting for the error in the cyclopropylcarbinyl system. Consequently, these results indicate that the cleavage of spiropentylcarbinyl radical should take place about 10^{10} s^{-1} [28] and that by tuning this system one may be able to achieve extraordinarily fast isomerization rates. Experiments to test this prediction are currently underway.

Conclusion

Two 4-butylspiropentylcarbinyl radicals (**18a** and **18b**) were formed and their rearrangements were studied. The composition

(22) For previous computations on cyclopropylcarbinyl and homoallyl radical, see (a) Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc*. **2000**, *122*, 2988. (b) Tian, F.; Bartberger, M. D.; Dolbier, W. R., Jr. *J. Org. Chem*. **1999**, *64*, 540. (c) Smith, D. M.; Nicolaides, A.; Golding, B. T.; Radom, L. *J. Am. Chem. Soc*. **1998**, *120*, 10223. (d) Martinez, F. N.; Schlegel, H. B.; Newcomb, M. *J. Org. Chem*. **1998**, *63*, 3618. (e) Johnson, W. T. G.; Borden, W. T. *J. Am. Chem. Soc*. **1997**, *119*, 5930. (f) Martinez, F. N.; Schlegel, H. B.; Newcomb, M. *J. Org. Chem*. **1996**, *61*, 8547. (g) Francoise, D. *THEOCHEM* **1986**, *29*, 65. (h) Quenemoen, K.; Borden, W. T.; Davidson, E. R.; Feller, D. *J. Am. Chem. Soc*. **1985**, *107*, 5054.

(23) We were unable to locate the UMP2(fc)/6-31G(d) structure for homoallyl radical using standard procedures including the analytical calculation of force constants at each step along the geometry optimization. Given this difficulty, the structure was optimized at the QCISD level with the 6-31G(d) basis set; this optimization proceeded without trouble. This problem previously has been noted in ref 22c.

(24) An alternative value of −5.4 ± 0.1 kcal mol^{-1} apparently at 0 K also has been reported (ref 19f). This energy difference is based on an updated value for the rate of the ring opening of cyclopropylcarbinyl radical (ref 20 g), but the original rate for the ring closure of homoallyl radical is reported in ref 20c. For consistency sake, we have compared our computational results to the original energy difference given by Effio et al. (−3.1 kcal mol^{-1}) in ref 18b, but in either case there is good accord with experiment.

(25) Dunning, T. H. *J. Chem. Phys*. **1989**, *90*, 1007.

(26) Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys*. **1991**, *94*, 7221.

(27) The G2 $H_{298\ K}$ energies are −156.197223 (**39**), −156.185032 (1-methylcyclopropyl radical), and −156.854097 (methylcyclopropane).

(28) If one uses $E_a = 4.0$ and $\log A = 13.15$ as determined for cyclopropylcarbinyl radical (ref 18h and 18i) then $k = 1.6 \times 10^{10}$ s^{-1} at 25 °C.

Table 2. Computed Relative Energies of Spiropentylcarbinyl (**42**), 1-Vinylcyclopropylcarbinyl (**43**), and 1-Allylcyclopropyl (**44**) Radicals, and the Ring Opening Transition States of **42** at Different Computational Levels

	rel. energies[b]			barriers[b]		corr. barriers[b,c]	
method[a]	**42**	**43**	**44**	TS (**42** → **43**)	TS (**42** → **44**)	TS (**42** → **43**)	TS (**42** → **44**)
HF/6-31G(d)	12.2	0	7.4	7.0	13.5	4.1	10.6
MP2/6-31G(d)//HF/6-31G(d)	8.1 (8.7)	0	10.1 (10.6)	10.8 (4.2)	18.6 (11.3)	3.0 (3.6)	10.8 (10.7)
MP2/6-31G(d)	6.1 (6.5)	0	10.0 (10.5)	12.7 (5.1)	19.7 (12.5)	4.0 (3.4)	11.0 (10.8)
MP2/cc-pVDZ	7.9 (8.1)	0	10.7 (11.1)	11.3 (5.0)	18.8 (11.8)	2.7 (3.5)	10.4 (10.3)
MP3/cc-pVDZ	9.3 (9.5)	0	9.0 (9.3)	10.5 (5.8)	17.1 (11.8)	3.7 (3.8)	10.3 (9.8)
MP4(SDQ)/cc-pVDZ	9.6	0	9.1	9.2	15.5	4.0	10.3
CCSD/cc-pVDZ	10.0	0	9.1	7.1	12.8	4.4	10.1
CCSD(T)/cc-pVDZ	10.3	0	9.5	6.2	11.8	4.0	9.6

[a] All of the calculations using the cc-pVDZ basis set were carried out on MP2/6-31G(d) optimized structures. [b] Parenthetical values are at the PMP2 or PMP3 level. [c] These barriers have been empirically corrected for the difference between experiment and calculation in the cyclopropylcarbinyl system.

and ratio of the ring-opened products does not depend on the stereochemistry of the remote stereocenter and preferential cleavage of the C1−C2 bond affords a cyclopropylcarbinyl radical, which undergoes a second ring opening to give the observed products. These results are in accord with high-level ab initio calculations which indicate that the ring opening of spiropentylcarbinyl radical should be extremely facile (k_{25} °C $\sim 10^{10}$ s^{-1}) and that formation of 1-vinylcyclopropylcarbinyl radical via C1−C2 bond cleavage should be $\sim 10^4$ times more rapid than C1−C3 homolysis to give 1-allylcyclopropyl radical. This ring system provides an attractive opportunity for designing extremely short-lived radical intermediates. The above results also allow us to propose that the irreversible inactivation of MCAD and SCAD by SPA-CoA proceeds via the covalent modification of FAD by a primary cyclopropylcarbinyl radical (**5**) rather than by a tertiary cyclopropyl radical (**4**). The two common alkylation sites on FAD, N_5 and C_{4a}, are each receptive to covalent bond formation with the reactive intermediate **5** to yield **37** and **38**, respectively. The carbon connecting **5** to the flavin coenzyme was shown to have a chemical shift of 42 ppm in the ^{13}C NMR spectrum,[6] and this is consistent with a *N*-linked saturated carbon atom. This early spectral data, along with the above chemical and computational results, provide strong evidence indicating that **37** is the most likely structure for the modified FAD adduct.[29]

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded on IBM NR/300 or Varian U-300 or U-500 spectrometers. Chemical shifts are reported on the δ-scale relative to tetramethylsilane as an internal standard. High-resolution mass spectral analyses were performed with a Finnigan MAT 95 mass spectrometer. Tandem gas chromatography−low resolution mass spectrometry (GC−MS) using electron ionization (EI, 70 eV) was carried out on a HP-5890 series II gas chromatograph and 5971A mass selective detector with a HP-1 12 m × 0.2 mm cross-linked dimethylsilicone gum-bonded phase capillary column. Instrument parameters were as follows: He flow rate, 0.65 mL/min; injection temperature, 250 °C; initial oven temperature, 50 °C for 2 min; temperature ramp, 20 °C/min; final temperature, 250 °C. Flash column chromatography was performed on columns of various diameters with J. T. Baker (230−400 mesh) silica gel. Medium-pressure liquid chromatography (25−60 psi) was carried out with the same silica gel as was used for flash chromatography in hand-packed columns along with a Fluid Metering Inc. pump. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm Masherey-Nagel silica gel plates. The ratio of solvents for solvent systems is reported as a volume/volume ratio. TLC spots were visualized either with UV light (254 nm) or by dipping the plates into staining solutions of vanilin/methanol/ H_2SO_4 (0.75:97.75:1.5) or phosphomolybdic acid (7% EtOH solution) and then heating them. The drying reagent used after routine workup was anhydrous magnesium or sodium sulfate. All reagents were purchased from Aldrich. Reactions requiring anhydrous conditions were performed under an atmosphere of dry Ar in oven-dried glassware. Tetrahydrofuran, ether, and methylene chloride were dried over Al_2O_3, and *n*-BuLi was titrated using diphenylacetic acid.

2-Octyn-1-ol (8). To a stirred solution of 7.81 g (81.2 mmol) of 1-heptyne (**7**) in 170 mL of dry THF and 42 mL (3 × 81.2 mmol) of HMPA at −30 °C was added dropwise 45 mL (90 mmol) of a 2.0 M solution of *n*-BuLi in hexanes. The reaction mixture was stirred at this temperature for 1 h, and then a suspension of 11.8 g (5 × 81.2 mmol) of previously well-dried paraformaldehyde in 50 mL of THF was added in one portion. The solution was stirred for 2 h at −30 °C, and then 15 mL of a saturated solution of NH_4Cl was added and the reaction mixture was allowed to warm to room temperature. Pentane (200 mL) was added and the resulting solution was washed first with brine (2 × 50 mL) and then with water (2 × 20 mL). The aqueous material was extracted with pentane (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$. Solvent removal was carried out under reduced pressure (∼15−20 Torr) using a long Vigreux column (25 cm), and then the residue was distilled under vacuum through a short (8 cm) Vigreux column to afford 9.2 g (90%) of the title compound (bp = 55−58 °C/0.5 Torr, lit. bp = 51 °C/0.25 Torr[15]).

***(Z)*-3-Iodooct-2-en-1-ol (9).** To a stirred solution of 3.24 g (25.7 mmol) of 2-octyn-1-ol (**8**) in 320 mL of dry THF was added 32.3 mL of a 3.4 M solution (109.8 mmol) of sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al) in toluene at 0 °C. The reaction mixture was stirred at this temperature for 72 h, and then 29.8 mL (306 mmol) of dry EtOAc was added slowly so that the temperature stayed between 0 and 5 °C. After stirring for an additional 20 min at 0 °C, the solution was cooled to −78 °C and 30.0 g of iodine (118 mmol) in 180 mL of dry THF was added via cannula. The reaction was stirred for 2 h at −78 °C before being allowed to warm to room temperature and being quenched with 300 mL of a concentrated Na_2SO_3 solution (1:1 saturated Na_2SO_3 to H_2O). The resulting layers were separated, the aqueous material was extracted with ether (3 × 200 mL), and the combined organic layers were washed with concentrated Na_2SO_3, saturated $NaHCO_3$, saturated NH_4Cl, and brine. Sodium sulfate was used to dry the organic solution, and then the solvent was removed under reduced pressure (∼15−20 Torr). Separation of the residue by MPLC using a 1:8 EtOAc/hexanes mixture afforded 4.73 g (72%) of the title compound and 0.24 g (3.7%) of (*E*)-2-iodooct-2-en-1-ol (**10**). **9**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz), 1.19−1.37 (m, 4H), 1.53 (quintet, 2H, J = 7.5 Hz), 1.60 (t, 1H, J = 6.0 Hz, OH), 2.49 (dt, 2H, J = 1.25 and 7.5 Hz), 4.20 (t, 2H, J = 6.0 Hz), 5.84 (tt, 1H, J = 1.25 and 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.4 (CH_2), 28.9 (CH_2), 30.4 (CH_2), 45.2 (CH_2), 67.3 (CH_2), 111.0 (C), 133.3 (CH). HRMS-CI (NH_3) calcd for $C_8H_{15}OI$ (M^+) 254.0169, found 254.0175. **10**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz), 1.32 (m,

(29) For related work, see: (a) Mitchell, D. J.; Nikolic, D.; van Breemen, R. B.; Silverman, R. B. *Bioorg Med. Chem. Lett.* **2001**, *11*, 1757. (b) Mitchell, D. J.; Nikolic, D.; Rivera, E.; Sablin, S. O.; Choi, S.; van Breemen, R. B.; Singer, T. P.; Silverman, R. B. *Biochemistry* **2001**, *40*, 5447.

4H), 1.43 (quintet, 2H, J = 7.0 Hz), 1.89 (t, 1H, J = 7.0 Hz, OH), 2.16 (q, 2H, J = 7.0 Hz), 4.25 (dq, 2H, J = 1.25 and 7.0 Hz), 5.89 (tt, 1H, J = 1.25 and 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2), 27.9 (CH_2), 31.4 (CH_2), 35.7 (CH_2), 71.8 (CH_2), 108.1 (C), 136.8 (CH).

(*Z*)-1-Iodo-1-pentyl-2-hydroxymethylcyclopropane (11). A solution of 5.2 mL (65 mmol) of CH_2I_2 in 260 mL of CH_2Cl_2 was stirred and 32.5 mL of a 1.0 M solution of Et_2Zn in hexanes (32.5 mmol) was added dropwise over a period of 15 min during which time a white precipitate formed. The resulting solution was cooled to −78 °C, and 8.09 g (31.85 mmol) of (*Z*)-3-iodooct-2-en-1-ol (**9**) in 140 mL of CH_2Cl_2 was added. After stirring the reaction mixture at −20 °C for 15 min, 4.88 mL of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.15 × 32.5 mmol) was added. The resulting solution was stirred overnight at −18 °C; then it was cooled to −40 °C, and then it was poured into 1.0 l of a saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL) and the combined organic layers were washed with NH_4Cl and brine before being dried over $MgSO_4$. Solvent removal was carried out under reduced pressure (∼15−20 Torr) through a 25-cm Vigreux column, and the residue was separated by MPLC using a 1:8 EtOAc/hexanes mixture to afford 4.18 g (49%) of **11** and 1.15 g of starting material. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.53 (m, 1H), 0.90 (t, 3H, J = 7.0 Hz), 0.90 (m, 1H), 1.01 (dd, 1H, J = 6.5 and 10.0 Hz), 1.26−1.34 (m, 4H), 1.44−1.56 (m, 3H), 1.68 (m, 1H), 1.89 (dd, 1H, J = 4.5 and 9.0 Hz, OH), 3.49 (ddd, 1H, J = 4.5, 9.0, and 12.0 Hz), 3.98 (ddd, 1H, J = 5.0, 9.0, and 12.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 18.8 (C), 21.9 (CH_2), 22.7 (CH_2), 26.3 (CH), 29.2 (CH_2), 30.9 (CH_2), 45.6 (CH_2), 69.6 (CH_2). HRMS-CI (NH_3) calcd for $C_9H_{21}NOI$ $(M + NH_4)^+$, 286.0699; found 286.0683.

(*E*)-1-Pentylidene-2-hydroxymethylcyclopropane (12a) and (*Z*)-1-pentyliden-2-hydroxy-methylcyclopropane (12b). To a stirred solution of 7.89 g (29.4 mmol) of 1-iodo-1-pentyl-2-hydroxymethylcyclopropane (**11**) in 10 mL of dried DMSO was added dropwise 67.0 mL of a 1.0 M solution of *t*-BuOK in DMSO. The reaction mixture was stirred overnight at room temperature and then was poured onto a mixture of ice-cold water and pentane. Solid NaCl was added and the product was extracted with pentane (3 × 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Solvent removal through a 25-cm Vigreux column was carried out under reduced pressure (∼15−20 Torr) leaving 4.10 g (99%) of a 1:1 mixture of **12a** and **12b** as determined by GC−MS. Purification and separation of the two isomers was carried out by MPLC using a 1:8 EtOAc/hexanes solvent mixture to afford 1.50 g (36%) of **12b** and 1.52 g (38%) of **12a**. **12a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (m, 1H), 0.90 (t, 3H, J = 7.0 Hz), 1.27 (tq, 1H, J = 8.5 and 1.5 Hz), 1.33 (m, 2H), 1.42 (m, 2H), 1.63 (br s, 1H, OH), 1.76 (m, 1H), 2.17 (m, 2H), 3.48 (dd, 1H, J = 7.5 and 11.0 Hz), 3.58 (dd, 1H, J = 6.0 and 11.0 Hz), 5.85 (tq, 1H, J = 7.0 and 2.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.4 (CH_2), 14.0 (CH_3), 17.6 (CH_2), 22.3 (CH_2), 31.4 (CH_2), 31.5 (CH_2), 66.0 (CH_2), 119.8 (CH), 122.9 (C). HRMS-CI (NH_3) calcd for $C_9H_{20}NO$ $(M + NH_4)^+$ 158.1546, found 158.1548. **12b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz), 0.92 (m, 1H), 1.28 (m, 1H), 1.33 (m, 2H), 1.39 (m, 2H), 1.62 (dd, 1H, J = 4.0 and 6.0 Hz, OH), 1.77 (m, 1H), 2.16 (m, 2H), 3.40 (ddd, 1H, J = 4.0, 8.5, and 11.0 Hz), 3.73 (ddd, 1H, J = 6.0, 6.0, and 11.0 Hz), 5.80 (tq, 1H, J = 7.0 and 2.0 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.7 (CH_2), 14.0 (CH_3), 17.8 (CH), 22.3 (CH_2), 31.8 (CH_2), 32.0 (CH_2), 65.7 (CH_2), 120.4 (CH), 122.8 (C). HRMS-CI (NH_3) calcd for $C_9H_{20}NO$ $(M + NH_4)^+$, 158.1546; found 158.1552.

(*Z*)-4-Butyl-1-hydroxymethylspiropentane (13b). To a stirred solution of 1.12 mL (14.0 mmol) of CH_2I_2 in 56 mL of CH_2Cl_2 was added dropwise 7.0 mL (7.0 mmol) of a 1.0 M solution of Et_2Zn in hexanes over a period of 15 min during which time a white precipitate formed. The reaction mixture was cooled to −78 °C and 0.980 g (7.0 mmol) of (*Z*)-1-(pentylidene)-2-hydroxy-methylcyclopropane (**12b**) in 35 mL of CH_2Cl_2 was added. The resulting solution was stirred at −20 °C for 15 min, at the end of which time 1.05 mL (0.15 × 7.0 mmol) of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 was added and stirring was continued at −18 °C overnight. The reaction mixture was then cooled to −40 °C and poured into 200 mL of a saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic layers were washed with NH_4Cl and brine. Removal of the solvent was carried out through a 25-cm Vigreux column under reduced pressure (∼15−20 Torr) without having dried the solution. A 5:1 mixture of acetone and water (30 mL) was added to the residue, and then 6 mL of a 1.0 M solution of methylmorpholine *N*-oxide (*N*-MMO) in water was added along with a catalytic amount of OsO_4. The reaction mixture was stirred overnight, and then the volatile solvent was removed under reduced pressure (∼15−20 Torr) through a 25-cm Vigreux column. Extraction of the aqueous residue with pentane (3 × 30 mL) was followed by washing the combined organic material with brine and drying it with $MgSO_4$. Removal of the solvent was carried out by distillation at atmospheric pressure with a short (10-cm) Vigreux column, and the residue was purified by MPLC using a 1:8 EtOAc/hexanes mixture to yield 0.842 g (78%) of the title compound (**13b**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.42 (t, 1H, J = 4.25 Hz), 0.64 (t, 1H, J = 4.25 Hz), 0.83 (dd, 1H, J = 4.25 and 7.5 Hz), 0.89 (t, 3H, J = 7.0 Hz), 0.96 (dd, 1H, J = 4.25 and 7.5 Hz), 1.03 (m, 1H), 1.19−1.34 (m, 6H), 1.39 (m, 1H), 1.52 (m, 1H, OH), 3.54 (dd, 1H, J = 7.0 and 10.5 Hz), 3.60 (dd, 1H, J = 7.0 and 10.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.8 (CH_2), 11.0 (CH_2), 14.2 (CH_3), 16.8 (CH), 17.4 (CH), 19.4 (C), 22.7 (CH_2), 31.5 (CH_2), 32.7 (CH_2), 66.9 (CH_2). HRMS-CI (NH_3) calcd for $C_{10}H_{22}NO$ $(M + NH_4)^+$, 172.1702; found 172.1717.

(*E*)-4-Butyl-1-hydroxymethylspiropentane (13a). Reacting 1.12 g (8.0 mmol) of (*E*)-1-(pentylidene)-2-hydroxymethylcyclopropane (**12a**), 1.28 mL (16 mmol) of CH_2I_2, 8.0 mL (8.0 mmol) of a 1.0 M solution of Et_2Zn in hexanes, and 1.2 mL of a 1.0 M solution of $TiCl_4$ (0.15 × 8.0 mmol) in CH_2Cl_2 as in the previously described procedure afforded 0.92 g (75%) of the title compound (**13a**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.36 (t, 1H, J = 4.25 Hz), 0.52 (t, 1H, J = 4.25 Hz), 0.89 (t, 3H, J = 7.0 Hz), 0.91 (dd, 1H, J = 4.25 and 7.5 Hz), 0.96 (dd, 1H, J = 4.25 and 7.5 Hz), 1.03 (m, 1H), 1.24−1.35 (m, 6H), 1.39 (m, 1H), 1.50 (m, 1H, OH), 3.52 (dd, 1H, J = 7.0 and 10.5 Hz), 3.61 (dd, 1H, J = 7.0 and 10.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3 (CH_2), 9.7 (CH_2), 14.2 (CH_3), 16.9 (CH), 19.4 (C), 19.8 (CH), 22.6 (CH_2), 31.5 (CH_2), 32.3 (CH_2), 66.5 (CH_2). HRMS-CI (NH_3) calcd for $C_{10}H_{22}NO$ $(M + NH_4)^+$, 172.1702; found 172.1734 and calcd for $C_{10}H_{20}N$ $(M + NH_4 - H_2O)^+$, 154.1597; found 154.1592.

(*Z*)-4-Butyl-1-bromomethylspiropentane (14b). To a well-stirred solution of 0.37 g (2.4 mmol) of (*Z*)-4-butyl-1-hydroxymethylspiropentane (**13b**) and 1.16 g (3.6 mmol) of carbon tetrabromide in 0.48 mL of dry CH_2Cl_2 was added dropwise via a syringe over a 4-h period a solution of 0.63 g (2.4 mmol) of triphenylphosphine in 0.69 mL of dry CH_2Cl_2 at room temperature. After an additional 1 h of stirring, the reaction mixture was treated with 40 mL of pentane, and the resulting precipitate (triphenylphosphine oxide) was removed by filtration and washed with pentane (2 × 5 mL). The combined pentane solutions were washed with 5% $NaHCO_3$ and brine and then were dried over $MgSO_4$. After the solvent was removed by distillation at atmospheric pressure using a short (10-cm) Vigreux column, a small impurity of $CHBr_3$ was removed under vacuum at ∼0.3 Torr for 2 h. The residue was passed through a short silica gel column using pentane as the eluent to afford 0.52 g (99%) of title compound (**14b**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.63 (t, 1H, J = 4.5 Hz), 0.72 (t, 1H, J = 4.5 Hz), 0.81 (dd, 1H, J = 4.5 and 7.5 Hz), 0.89 (t, 3H, J = 7.0 Hz),1.08 (m, 1H), 1.15 (dd, 1H, J = 4.5 and 7.5 Hz), 1.30−1.38 (m, 6H), 1.59 (dddd, 1H, J = 4.5, 7.0, 7.0, and 9.0 Hz), 3.25 (dd, 1H, J = 9.0 and 10.0 Hz),), 3.61 (dd, 1H, J = 7.0 and 10.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.1 (CH_2), 14.4 (CH_3), 15.4 (CH_2), 18.0 (CH), 18.1 (CH), 22.8 (CH_2), 23.5 (C), 31.7 (CH_2), 32.2 (CH_2), 39.5 (CH_2). HRMS-CI (NH_3) calcd for $C_{10}H_{18}Br$ $(M + H)^+$, 217.0592; found 217.0589.

(*E*)-4-Butyl-1-bromomethylspiropentane (14a). Reacting 0.455 g (2.95 mmol) of (*E*)-4-butyl-1-hydroxymethylspiropentane (**13a**), 1.47 g (4.43 mmol) of carbon tetrabromide in 0.6 mL of CH_2Cl_2, and 0.722 g (2.95 mmol) of triphenylphosphine in 0.85 mL of CH_2Cl_2 as was previously described afforded 0.637 g (99%) of the title compound (**14a**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) 0.36 (br t, 1H), 0.61 (t, 1H, J = 4.25 and 4.25 Hz), 0.89 (t, 3H, J = 7.0 Hz), 1.08 (m, 2H), 1.15 (dd, 1H, J = 4.25 and 7.5 Hz), 1.25−1.34 (m, 6H), 1.59 (dddd, 1H, J = 4.25, 7.5, 7.5, and 8.5 Hz), 3.33 (dd, 1H, J = 8.5 and 10.0 Hz), 3.50 (dd, 1H, J = 7.5 and 10.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) 9.3 (CH_2), 12.9 (CH_2), 14.3 (CH_3), 17.9 (CH), 20.4 (CH), 22.8 (CH_2), 23.8 (C), 31.7 (CH_2), 32.3 (CH_2), 39.1 (CH_2). HRMS-CI (NH_3) calcd for $C_{10}H_{16}Br$ $(M - H)^+$, 215.0436; found 215.0443.

(*Z*)-4-Butyl-1-(1-butenyl)spiropentane (16b). To a stirred solution of 0.51 g (3.31 mmol) of (*Z*)-4-butyl-1-hydroxymethylspiropentane (**13b**) in 20 mL of CH_2Cl_2 was added 0.504 g (1.3 × 3.31 mmol) of *N*-MMO. The reaction mixture was cooled to 0 °C, and 0.07 g of TPAP together with 200 mg of crushed 4 Å molecular sieves were added and the solution was stirred for 2 h. After the reaction was complete (as indicated by TLC), the solution was filtered through a short silica gel column using 50 mL of CH_2Cl_2 and then 10 mL of EtOAc. Removal of the solvent was carried out at reduced pressure (∼15−20 Torr) through a 10-cm Vigreux column at 30 °C. The residue was dried under vacuum (0.2 Torr) over a 15-min period, dissolved in 7 mL of dry THF and submitted to the next step without further purification.

To a stirred solution of 3.82 g (9.92 mmol) of *n*-propyltriphenylphosphonium bromide in 50 mL of dry THF was added 9.92 mL (9.92 mmol) of a 1.0 M solution of NaHMDS in THF at 0 °C under an argon atmosphere. The reaction mixture was stirred for 15 min at 0 °C, and then the aldehyde (**15b**) in 7 mL of THF from the previous step was added dropwise. Stirring was continued as the reaction mixture was allowed to warm to room temperature over 3 h. After the reaction was complete (as indicated by TLC), the mixture was cooled to 0 °C; 100 mL of cold water was added and the solution was extracted with pentane (3 × 15 mL). The combined organic extracts were washed with brine (2 × 5 mL) and dried over Na_2SO_4. Pentane was removed by distillation through a 10-cm Vigreux column at atmospheric pressure; the residue was filtered and the solid triphenylphosphine oxide and unreacted *n*-propyltriphenylphosphonium bromide were rinsed with pentane (3 × 5 mL). The solvent was removed again by distillation through a 10-cm Vigreux column at atmospheric pressure. The resulting residue was dried under vacuum (0.2 Torr) for 15 min to give 0.494 g (84%) of **16b** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.38 (t, 1H, J = 4.5 Hz), 0.72 (t, 1H, J = 4.25 Hz), 0.81 (dd, 1H, J = 4.5 and 7.5 Hz), 0.90 (t, 3H, J = 7.0 Hz), 0.99 (t, 3H, J = 7.0 Hz), 1.03 (m, 1H), 1.18 (dd, 1H, J = 4.0 and 8.0 Hz), 1.29−1.37 (m, 6H), 1.89 (m, 1H), 2.10−2.17 (m, 2H), 4.19 (br t, 1H, J = 10.5 Hz), 5.35 (dt, 1H, J = 10.5 and 7.0 Hz). ^{13}C NMR(75 MHz, $CDCl_3$) δ 10.1 (CH_2), 14.1 (CH_3), 14.2 (CH), 14.5 (CH_3), 15.1 (CH_2), 17.5 (CH), 20.9 (CH_2), 21.9 (C), 22.6 (CH_2), 31.5 (CH_2), 32.3 (CH_2), 130.2 (CH), 132.2 (CH). HRMS-CI (NH_3) calcd for $C_{13}H_{23}$ $(M + H)^+$, 179.1801; found 179.1792.

(*E*)-4-Butyl-1-(1-butenyl)spiropentane (16a). Reacting 0.79 g (5.13 mmol) of (*E*)-4-butyl-1-hydroxymethylspiropentane (**13a**), 0.781 g (1.3 × 5.13 mmol) of *N*-MMO, 0.1 g of TPAP, and 0.35 g of crushed 4 Å molecular sieves yielded the corresponding aldehyde (**15a**) as described in the previous experiment. This material was used in the subsequent reaction without further purification. Following the same procedure as described for **16b** and using 5.93 g (15.39 mmol) of *n*-propyltriphenylphosphonium bromide and 15.4 mL of a 1.0 M solution of NaHMDS in THF gave 0.77 g (84%) of **16a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.35 (t, 1H, J = 4.25 Hz), 0.59 (t, 1H, J = 4.25 Hz), 0.85 (dd, 1H, J = 4.25 and 8.0 Hz), 0.91 (t, 3H, J = 7.0 Hz), 0.98 (t, 3H, J = 7.0 Hz), 1.03 (m, 1H), 1.19 (dd, 1H, J = 4.0 and 8.0 Hz), 1.28−1.37 (m, 6H), 1.89 (m, 1H), 2.07−2.18 (m, 2H), 4.92 (t, 1H, J = 10.0 Hz), 5.34 (dt, 1H, J = 11.0 and 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.2 (CH_2), 12.4 (CH_2), 14.2 (CH_3), 14.6 (CH_3), 16.7 (CH), 17.3 (CH), 21.0 (CH_2), 22.0 (C), 22.7 (CH_2), 31.6 (CH_2), 32.2 (CH_2), 130.3 (CH), 131.7 (CH). HRMS-CI (NH_3) calcd for $C_{13}H_{23}$ $(M + H)^+$, 179.1801; found 179.1804.

(*Z*)-1,4-Dibutylspiropentane (17b). To a solution of 0.178 g (1.0 mmol) of (*Z*)-4-butyl-1-(1-butenyl)spiropentane (**16b**) in 36 mL of MeOH was added 2.63 mL (42.0 mmol) of 98% hydrazine and 1 drop of a 1% aqueous solution of $CuSO_4$. The reaction mixture was cooled to 0 °C and maintained at this temperature for 24 h before 10.86 mL (48 mmol) of 30% aqueous H_2O_2 was added via syringe at a rate of 0.49 mL/hr. After the reaction was complete (as indicated by TLC), 120 mL of cold water was added and the solution was extracted with pentane (3 × 10 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried over Na_2SO_4. Atmospheric distillation of the solvent through a short Vigreux column left 0.148 g (82%) of the title compound (**17b**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.38 (m, 2H), 0.74 (dd, 1H, J = 4.0 and 7.5 Hz), 0.83 (dd, 1H, J = 4.0 and 7.5 Hz), 0.89 (m, 6H), 0.99 (m, 2H), 1.24−1.39 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.8 (CH_2), 12.7 (CH_2), 14.1 (CH_3), 14.2 (CH_3), 15.2 (CH), 17.8 (CH), 20.6 (C), 22.66 (CH_2), 22.71 (CH_2), 31.6 (CH_2), 32.6 (CH_2), 32.9 (CH_2) [1 line missing, presumably, due to overlapping peaks at 31.6]. HRMS-CI (NH_3) calcd for $C_{13}H_{25}$ $(M + H)^+$, 181.1958; found 181.1961.

(*E*)-1,4-Dibutylspiropentane (17a). Using the aforementioned procedure, reacting 0.178 g (1.0 mmol) of (*E*)-4-butyl-1-(1-butenyl)-spiropentane (**16a**) led to the formation of 0.152 g (84%) of **17a** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.25 (t, 2H, J = 4.0 Hz), 0.84 (dd, 2H, J = 4.0 and 7.5 Hz), 0.89 (t, 6H, J = 7.0 Hz), 0.96 (m, 2H), 1.26−1.34 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.9 (CH_2), 14.2 (CH_3), 17.7 (CH), 20.7 (C), 22.6 (CH_2), 31.7 (CH_2), 32.4 (CH_2). HRMS-CI (NH_3) calcd for $C_{13}H_{25}$ $(M + H)^+$, 181.1958; found 181.1956.

(*E*)-4-Butyl-1-methylspiropentane (19a). A solution of 0.0434 g (0.2 mmol) of (*E*)-4-butyl-1-bromomethylspiropentane (**14a**) in 1.0 mL of ether was added to a suspension of 0.076 g (2.0 mmol) of lithium aluminum hydride in 3 mL of ether, and the reaction mixture was stirred at room temperature overnight. Upon cooling to 0 °C, the reaction was quenched by slowly adding 2 mL of water. Pentane (5 mL) was added to the resulting suspension and the mixture was filtered. The solid residue was washed with pentane (2 × 1 mL), the combined organic material was dried over $MgSO_4$, and the solvent was removed by distillation through a 20-cm Vigreux column at atmospheric pressure. Column chromatography on silica gel with pentane afforded 8.7 mg (32%) of **19a** after removing the solvent by distillation through a 20-cm Vigreux column at atmospheric pressure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.21 (t, 1H, J = 4.0 Hz), 0.24 (t, 1H, J = 4.0 Hz), 0.80 (dd, 1H, J = 4.0 and 9.0 Hz), 0.86−0.88 (m, 2H), 0.89 (t, 3H, J = 7.0 Hz), 0.99 (m, 1H), 1.01−1.03 (m, 3H), 1.26−1.38 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.8, 11.3, 12.0, 14.4, 17.2, 18.1, 22.9, 29.9, 31.9, 32.7. HRMS-CI (NH_3) calcd for $C_{10}H_{17}$ $(M - H)^+$, 137.1330; found 137.1322, calcd for $C_{10}H_{22}N$ $(M + NH_4)^+$, 156.1752; found 156.1745.

(*Z*)-4-Butyl-1-methylspiropentane (19b). Carrying out the same procedure on the same scale only starting with (*Z*)-4-butyl-1-bromomethylspiropentane **(14b)** afforded 12.2 mg (44%) of **19b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.32 (t, 1H, J = 4.0 Hz), 0.34 (t, 1H, J = 4.0 Hz), 0.73 (dd,1H, J = 4.0 and 7.5 Hz), 0.86 (m, 1H), 0.89 (t, 3H, J = 7.0 Hz), 0.93 (m, 1H), 0.99−1.05 (m, 4H), 1.26−1.38 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.4, 9.8, 14.0, 14.4, 17.8, 18.4, 22.9, 29.9, 31.8, 32.8. HRMS-CI (NH_3) calcd for $C_{10}H_{17}$ $(M - H)^+$, 137.1330; found 137.1338, calcd for $C_{10}H_{22}N$ $(M + NH_4)^+$, 156.1752; found 156.1767.

(*E*)-2-Methylhept-2-en-1-ol (24a) and (*Z*)-2-Methylhept-2-en-1-ol (24b).[30] 1-Bromopropane (7.38 g, 60 mmol) in 35 mL of ether was slowly added over 40 min to 0.94 g (135 mmol) of lithium wire (3.2 mm diameter) in 10 mL of ether. The first 3 mL of the alkyl halide

(30) Lakomy, I.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 804.

solution was rapidly added at room temperature to initiate the reaction; the ethereal solution became cloudy and the lithium metal became shiny, and the rest of the material was added at −20 to −25 °C. After an additional hour at −20 °C, the alkyllithium was transferred to an addition funnel under a dry stream of argon and added over 1 h at −50 to −60 °C to 5.1 g (20 mmol) of CuI in 10 mL of ether. After stirring at −50 °C for 1 h, the brownish solution was warmed to −20 to −30 °C and 2.08 g (2.48 mmol) of 3,4-epoxy-3-methyl-1-butene was added dropwise to it. The reaction mixture was stirred for 1.5 h at −20 °C and quenched with saturated NH_4Cl at −30 °C. Aqueous ammonia (10%) was then added until a clear dark-blue solution resulted and the aqueous material was extracted with ether (3 × 20 mL). The combined organic material was washed with brine, dried over $MgSO_4$, and concentrated by distillation through a 20-cm Vigreux column at atmospheric pressure. The residue was distilled under vacuum (bp 52−53 °C at 0.1 Torr (lit. 57.7−59.0 °C under vacuum)[30] to give 2.66 g (84%) of a 77:23 mixture of **24a** and **24b** as a colorless oil. **(24a)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz), 1.28−1.36 (m, 4H), 1.55 (br. s, 1H), 1.66 (s, 3H), 2.03 (q, 2H, J = 7.0), 3.99 (s, 2H), 5.41 (tq, 1H, J = 7.5 and 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.2, 22.6, 27.5, 31.9, 69.2, 126.8, 134.8. HRMS-EI calcd for $C_8H_{16}O$ (M^+), 128.1201; found 128.1199. **(24b)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz), 1.28−1.36 (m, 4H), 1.45 (br s, 1H), 1.79 (q, 3H, J = 1.5 Hz), 2.03 (q, 2H, J = 7.0), 4.12 (s, 2H), 5.30 (tq, 1H, J = 7.0 and 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.1, 21.4, 22.5, 27.5, 32.4, 61.8, 129.0, 134.3.

(*Z*)-(2-Butyl-1-methylcyclopropyl)methanol (25a) and (*E*)-(2-Butyl-1-methylcyclo-propyl)methanol (25b). By reacting 0.512 g (4 mmol) of an isomeric mixture of (*E*)-2-methylhept-2-en-1-ol (**24a**) and (*Z*)-2-methylhept-2-en-1-ol (**24b**) with 0.64 mL (8 mmol) of CH_2I_2, 4.0 mL (4 mmol) of a 1.0 M solution of Et_2Zn in hexane, and 0.6 mL of a 1.0 M solution of $TiCl_4$ (0.6 mmol) in CH_2Cl_2 as described for the synthesis of **13b**, 0.482 g (85%) of **25a** and **25b** was obtained in a 78:22 ratio. **(25a)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.04 (t, 1H, J = 5.0 Hz), 0.51 (dd, 1H, J = 4.0 and 8.5 Hz), 0.58 (m, 1H), 0.89 (t, 3H, J = 7.0 Hz), 1.12 (s, 3H), 1.32−1.36 (m, 6H), 1.61 (br s, 1H), 3.31 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 15.4, 16.9, 22.1, 22.3, 22.8, 29.0, 32.6, 72.8. HRMS-CI (NH_3) calcd for C_9H_{17} ($M - OH$)$^+$, 125.1330; found 125,1328, calcd for $C_9H_{20}N$ ($M - H_2O + NH_4$)$^+$, 142.1596; found 142.1594, calcd for $C_9H_{22}NO$ ($M + NH_4$)$^+$, 160.1701; found 160.1689. **(25b)**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.10 (t, 1H, J = 5.0 Hz), 0.45 (dd, 1H, J = 4.5 and 8.5 Hz), 0.65 (m, 1H), 0.89 (t, 1H, J = 7.0 Hz), 1.13 (s, 3H), 1.20−1.42 (m, 6H), 1.45 (br s, 1H), 3.51 (d, 1H, J = 11.0 Hz), 3.58 (d, 1H, J = 11.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 17.9, 22.4, 22.8, 22.9, 25.3, 29.2, 32.7, 67.7. HRMS-CI (NH_3) calcd for $C_9H_{22}NO$ ($M + NH_4$)$^+$, 160.1701; found 160.1698, calcd for $C_9H_{20}N$ ($M - H_2O + NH_4$)$^+$, 142.1596; found 142.1598.

(*Z*)-(2-Butyl-1-methyl-1-cyclopropane)carboxaldehyde (26a) and (*E*)-(2-Butyl-1-methyl-1-cyclopropane)carboxaldehyde (26b). By reacting 0.379 g (2.67 mmol) of an isomeric mixture of **25a** and **25b** with 0.406 g (3.46 mmol) of *N*-MMO, 0.07 g of TPAP, and 0.15 g of crushed 4 Å molecular sieves as described for the synthesis of aldehyde **15b**, 0.360 g (96%) of **26a** and **26b** was obtained in a 78:22 ratio as a colorless volatile liquid. (**26a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (m, 1H), 0.90 (t, 3H, J = 7.0 Hz), 1.23 (s, 3H), 1.30−1.46 (m, 8H), 8.62 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2, 14.2, 20.2, 22.6, 25.2, 28.1, 31.9, 32.1, 203.1. HRMS-CI (NH_3) calcd for $C_9H_{17}O$ ($M + H$)$^+$, 141.1280; found 141.1271, calcd for $C_9H_{20}NO$ ($M + NH_4$)$^+$, 158.1545; found 158.1540. (**26b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.0 Hz), 1.11 dd, 1H, J = 4.5 and 7.5 Hz), 1.23 (s, 3H), 1.24−1.36 (m, 5H), 1.39 (m, 1H), 1.55 (m, 1H), 1.63 (m, 1H), 9.14 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 18.3, 22.5, 22.8, 28.7, 32.1, 32.26, 32.33, 203.6. HRMS-CI (NH_3) calcd for $C_9H_{17}O$ ($M + H$)$^+$, 141.1280; found 141.1283, calcd for $C_9H_{20}NO$ ($M + NH_4$)$^+$, 158.1545; found 158.1543.

(*Z*)-2-Butyl-1-methyl-1-vinylcyclopropane (20a) and (*E*)-2-Butyl-1-methyl-1-vinyl-cyclopropane (20b). Under a dry stream of argon, 4.09 mL of a 1.0 M solution of NaHMDS in THF was added dropwise to a stirred solution of 1.46 g (4.09 mmol) of methyltriphenyl-phosphonium bromide in 18 mL of THF at 0 °C. The reaction mixture was stirred for an additional 15 min at 0 °C. While maintaining the solution at 0 °C, 0.190 g (1.36 mmol) of an isomeric mixture of **26a** and **26b** in 2.5 mL of THF was added dropwise. Upon warming to room temperature, the solution was stirred for an additional 3 h before being cooled to 0 °C and quenched with 10 mL of cold water. The resulting suspension was extracted with pentane (3 × 10 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Distillation through a 20-cm Vigreux column at atmospheric pressure afforded a solid residue which was rinsed twice with 3-mL portions of pentane. Column chromatography on silica gel with pentane afforded 0.110 g (59%) of **20a** and **20b** in a 78:22 ratio as a colorless volatile liquid after removal of the solvent by distillation through a 20-cm Vigreux column at atmospheric pressure. **(20a)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.26 (m, 1H), 0.74 (m, 2H), 0.91 (t, 3H, J = 7.0 Hz), 1.16 (s, 3H), 1.30−1.45 (m, 6H), 4.83 (dd, 1H, J = 1.5 and 11.0 Hz), 4.91 (dd, 1H, J = 1.5 and 17.0 Hz), 5.41 (dd, 1H, J = 5.0 and 17.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 15.6, 21.3, 22.1, 22.8, 26.4, 29.2, 32.4, 108.5, 148.4. HRMS-CI (NH_3) calcd for $C_{10}H_{19}$ ($M + H$)$^+$, 139.1488; found 139.1481, calcd for $C_{10}H_{22}N$ ($M + NH_4$)$^+$, 156.1754; found 156.1757. **(20b)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.40 (t, 1H, J = 5.0 Hz), 0.69 (dd, 1H, J = 4.0 and 8.5 Hz), 0.77 (t, 1H, J = 7.0 Hz), 0.90 (t, 3H, J = 7.0 Hz), 1.18 (s, 3H), 1.20−1.40 (m, 6H), 4.99 (s, 1H), 5.02 (dd, 1H, J = 2.0 and 7.5 Hz), 5.69 dd (1H, J = 11.0 and 17.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 21.4, 22.5, 22.7, 23.2, 28.0, 29.5, 32.2, 111.8, 142.9. HRMS-CI (NH_3) calcd for $C_{10}H_{19}$ ($M + H$)$^+$, 139.1488; found 139.1487, calcd for $C_{10}H_{22}N$ ($M + NH_4$)$^+$, 156.1754; found 156.1751.

***trans*-1-Bromo-2-butylcyclopropane (28).** Following literature procedures,[11] 4.11 g (50 mmol) of 1-hexyne was converted to 4.02 g (36%) of **28** containing 5% of the cis isomer as determined by GC−MS. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (dt, 1H, J = 6.0 and 7.0 Hz), 0.91 (t, 3H, J = 7.0 Hz), 0.98 (m,1H), 1.21 (m, 1H), 1.22−1.42 (m, 6H), 2.60 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 16.1, 20.3, 22.6, 23.1, 31.1, 32.7. HRMS-CI (4% NH_3 in CH_4) calcd for $C_7H_{13}Br$ (M)$^+$, 176.0201 and 178.0181; found 176.0192 and 178.0179.

***cis*-1-Allyl-2-butylcyclopropane (21a) and *trans*-1-allyl-2-butyl-cyclopropane (21b).** Following a literature procedure,[31] 0.885 g (5 mmol) of *trans*-1-bromo-2-butyl-cyclopropane (**28**) containing 5% of the cis isomer was converted to 0.350 g (46%) of **21b** containing 5% of the cis isomer **(21a)** as determined by GC−MS. **(21b)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.22 (m, 2H), 0.47 (m, 2H), 0.89 (t, 3H, J = 7.0 Hz), 1.22−1.40 (m, 6H), 1.96 (m, 2H), 4.95−4.97 (m, 1H), 5.04−5.08 (m, 1H), 5.84−5.92 (m, 1H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 11.9, 14.5, 18.3, 19.0, 23.2, 32.4, 34.4, 38.8, 114.5, 139.0. HRMS-CI (NH_3) calcd for $C_{10}H_{17}$ ($M - H$)$^+$, 137.1331; found 137.1328, calcd for $C_{10}H_{22}N$ ($M + NH_4$)$^+$, 156.1754; found 156.1751.

4-Methyloct-1-en-3-ol (30). A few crystals of iodine were added to a solution of 5.2 g (0.21 mol) of magnesium turnings in 12 mL of anhydrous ether, and this mixture was warmed for 2 min with a heat gun under a dry argon atomosphere. 2-Bromohexane (16.5 g, 100 mmol) in 90 mL of ether was subsequently added in small portions until the reaction began, and then it was added dropwise so as to maintain a gentle reflux. After the addition was complete, the reaction mixture was heated for an additional 1 h and then acrolein (3.58 g, 64 mmol) was slowly added. After stirring the reaction mixture at room temperature for an additional 1 h, it was slowly poured into 70 mL of ice water. The resulting precipitate was dissolved by slowly adding a solution of 4.1 mL of concentrated sulfuric acid in 14 mL of water.

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After decanting this solution to remove the excess magnesium metal, the organic layer was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combained organic material was dried over $MgSO_4$, and the solvent was removed by distillation through a 20-cm Vigreux column at atmospheric pressure. Column chromatography of the residue on silica gel with CH_2Cl_2 afforded 3.10 g (34%) of **30** as a 1:1 mixture of isomers after removing the solvent by atmospheric distillation through a 20-cm Vigreux column. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.0 Hz), 0.89 (t, 3H, J = 7.0 Hz), 1.05−1.70 (m, 7H), 3.97 (m 1H), 5.15 (m, 1H), 5.22 (dt, 1H, J = 1.5 and 17.1 Hz), 5.86 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.5, 15.1, 23.16, 23.17, 29.6, 29.7, 32.1, 32.5, 38.67, 38.70, 77.0, 77.5, 115.4, 115.9, 139.32, 140.1 [the resonance at 14.3 corresponds to the terminal methyl groups from both isomers]. HRMS-CI (NH_3) calcd for $C_9H_{22}NO$ $(M + NH_4)^+$, 160.1701; found 160.1691, calcd for $C_9H_{20}N$ $(M - H_2O + NH_4)^+$, 142.1596; found 142.1586.

4-Methyloct-1-en-3-one (31). To a stirred solution of 3.42 g (24.08 mmol) of 4-methyloct-1-en-3-ol (**30**) in 150 mL of CH_2Cl_2 was added 7.34 g (62.65 mmol) of *N*-MMO at room temperature. The reaction mixture was cooled to 0 °C and 1.0 g (2.85 mmol) of TPAP together with 1.9 g of crushed 4 Å molecular sieves were added. The solution was then stirred for 48 h, and when the reaction was complete as indicated by TLC, it was filtered through a short silica gel column using CH_2Cl_2 as the eluent. Removal of the solvent at atmospheric pressure through a 20-cm Vigreux column gave 2.80 g (83%) of **31**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.0 Hz), 1.10 (d, 3H, J = 6.9 Hz), 1.20−1.40 (m, 4H), 1.67 (m, 2H), 2.79 (sextet, 1H, J = 6.9 Hz), 5.77 (dd, 1H, J = 1.5 and 10.5 Hz), 6.27 (dd, 1H, J = 1.5 and 17.5 Hz), 6.45 (dd, 1H, J = 10.5 and 17.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 16.6, 22.9, 29.6, 32.9, 43.6, 128.2, 135.4, 204.5. HRMS-CI (NH_3) calcd for $C_9H_{17}O$ $(M + H)^+$, 141.1280; found 141.1283, calcd for $C_9H_{20}NO$ $(M + NH_4)^+$, 158.1546; found 158.1551.

4-Methyl-3-methylene-1-octene (22). To 20 mL of a 1.0 M solution of (trimethylsilyl)methyl-lithium in pentane was added 20 mL of dry THF. This mixture was cooled to 0 °C and a solution of 500 mg (3.57 mmol) of 4-methyl-oct-1-en-3-one (**31**) in 40 mL of THF was added dropwise with stirring. After the reaction mixture was allowed to warm to room temperature and then refluxed for 3 h, it was cooled back to room temperature and stirred overnight. Distillation of the solvent at reduced pressure (200 Torr) was carried out with a bath temperature of 60 °C. The residue was diluted with 15 mL of anhydrous ether and 0.26 mL (3.57 mmol) of acetyl chloride was added dropwise with stirring. The reaction mixture was kept at room temperature overnight and then was hydrolyzed with a saturated aqueous ammonium chloride solution. The solid residue was filtered and washed with ether, and then the combined organic material was extracted with sodium bicarbonate and brine before being dried over magnesium sulfate. Atmospheric distillation of the solvent through a 20-cm Vigreux column afforded a liquid residue which was purified using a silica gel column and pentane as the eluent. Slow atmospheric distillation of pentane through a 40-cm Vigreux column afforded 80 mg (15%) of **22**; the GC yield was 31%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz), 1.08 (d, 3H, J = 6.9 Hz), 1.24−1.35 (m, 5H), 1.52 (m, 1H), 2.45 (sextet, 1H, J = 6.9 Hz), 4.95 (s, 1H), 5.03 (s, 1H), 5.04 (d, 1H, J = 10.8 Hz), 5.30 (dd, 1H, J = 0.9 and 17.4 Hz), 6.33 (ddd, 1H, J = 0.9, 10.8 and 17.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 20.5, 23.1, 29.9, 34.4, 36.2, 112.8, 113.2, 139.0, 152.3. HRMS-EI calcd for $C_{10}H_{18}$ $(M)^+$, 138.1408; found 138.1401.

Radical Rearrangement of Bromide 14a in Benzene.[12b,g] To a solution of 0.2 g (0.9 mmol) of bromide **14a** in 6 mL of benzene was added 0.38 mL (1.4 mmol) of tri-*n*-butyltin hydride followed by a catalytic amount of AIBN (ca. 0.005 g). The reaction mixture was refluxed for 2 h and after cooling to room temperature, 1.0 mL of CCl_4 and 1.0 mL of a saturated aqueous KF solution were added. The resulting mixture was cooled to 0 °C, stirred for 5 min, and allowed to sit at 0 °C without stirring for an additional 0.5 h. The organic layer was filtered through a plug of silica gel and the filtrate was concentrated under atmospheric pressure by distillation through a short Vigreux column. Purification of the residue was carried out by preparative GC (20% Squalane on Chrom W, column temperature 95 °C) to afford 3-methylene-1-nonene (**36**)[14] and 4-methyl-3-methylene-1-octene (**22**) in a 13:1 ratio. **36**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.6 Hz), 1.28−1.34 (m, 6H), 1.48 (ddd, 2H, J = 1.5, 7.4 and 7.4 Hz), 2.20 (ddd, 2H, J = 0.9, 7.4, and 7.4 Hz), 4.99 (m, 2H), 5.05 (dq, 1H, J = 10.8 and 1.2 Hz), 5.23 (dddd, 1H, J = 0.6, 0.6, 1.2, and 17.4 Hz), 6.37 (dd, 1H, J = 10.5 and17.4 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ 14.3, 22.9, 28.3, 29.5, 31.6, 32.0, 113.3, 115.7, 139.2, 146.8. HRMS-CI (NH_3) calcd for $C_{10}H_{19}$ $(M + H)^+$, 139.1488; found 139.1491. **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.9 Hz), 1.06 (d, 3H, J = 6.9 Hz) 1.24−1.33 (m, 5H), 1.52 (m, 1H), 2.43 (sextet, 1H, J = 6.9 Hz), 4.94 (s, 1H), 5.03 (s, 1H), 5.03 (d, 1H, J = 10.8 Hz), 5.28 (dd, 1H, J = 0.6 and 17.4 Hz), 6.33 (dd, 1H, J = 10.8 and 17.4 Hz).

Radical Rearrangement of Bromide 14b in Benzene. Bromide **14b** was subjected to the reduction conditions described for bromide **14a,** and 3-methylene-1-nonene (**36**) and 4-methyl-3-methylene-1-octene (**22**) were isolated by gas chromatography in a 13:1 ratio, respectively.

Radical Rearrangement of Bromides 14a and 14b in Neat Bu_3SnH.[12b,g] Bromide **14a** (or **14b**) (0.0103 g, 0.475 mmol) was placed into a 10-mL reaction tube, previously swept with dry argon. Neat Bu_3SnH (1.17 mL, 47.5 mmol) and 0.001 g of AIBN were added under argon, and the reaction tube was carefully closed and allowed to stir for 48 h at room temperature. After cooling to 0 °C, the reaction tube was opened, and 2.0 mL of CCl_4 was added. The reaction mixture was allowed to warm to room temperature overnight with stirring. A saturated aqueous solution of KF (4 mL) and 8 mL of ether were added and vigorously shaken for 2 h. The resulting mixture was filtered through Celite and the solid fluoride residue was washed with 2 mL of ether. The organic material was dried over $MgSO_4$ and analyzed by GC−MS before the solvent was removed by distillation through a 20-cm Vigreux column at atmospheric pressure. The residue was dissolved in pentane (1 mL) and the volatile compounds were purified (but not separated) by column chromatorgraphy using a 20-cm silica gel column eluted with pentane. Fractions with R_f values from 0.7 to 1.0 were collected and concentrated by distillation through a 20-cm Vigreux column at atmospheric pressure. The resulting material was then analyzed by GC−MS.

Computational Methods. All computations were carried out using Gaussian 98[32] installed on IBM and SGI workstations. Full geometry optimizations were carried out at the UHF, UMP2(fc), and UQCISD levels of theory with the 6-31G(d) basis set. Each stationary point was verified as being a minimum on the potential-energy surface by analytically (HF and MP2) or numerically (QCISD) calculating the vibrational frequencies. Zero-point energy corrections were made using scaling factors of 0.9135 (HF) and 0.9646 (MP2 and QCISD), while temperature adjustments to 298 K were made by scaling the vibrational frequencies by 0.8929 (HF) and 0.9427 (MP2 and QCISD).[33] Single-point energy determinations were carried out at the MP2, MP3, MP4(SDQ), CCSD, and CCSD(T) levels with the 6-31G(d), cc-pVDZ, and 6-311+G(2df,2pd) basis sets. In addition, G2[26] calculations were carried

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out on methylcyclopropane, cyclopropylcarbinyl radical, and homoallyl radical as described in the original reference.

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Supporting Information Available: Computed structures and absolute energies along with ^{1}H and ^{13}C NMR spectra for **14**, **17**, **19**−**22**, and **36** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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