Total Synthesis of (±)-Tetramethylmediterraneol B

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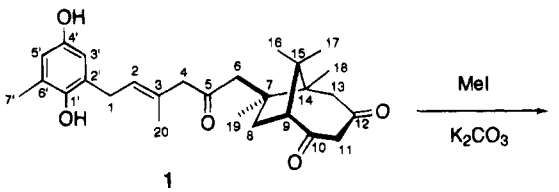
A diterpenoid having the structure proposed for the tetramethylated derivative **2** of mediterraneol B (**1**) has been synthesized in a stereocontrolled manner via coupling between the hydroquinone side chain **7** and the bicyclo[4.2.1]nonane core **8** followed by buildup of the 1,3-diketone functionality. The hydroquinone segment **7** was prepared easily according to the reported method. Synthesis of the key component **8** was undertaken starting from *tert*-butylcyclohexenone **11**. The cornerstone of the synthesis is the acid-catalyzed rearrangement of bicyclo[4.2.0]octanone **10** to the ketone **9** which has the bicyclononane skeleton and has clues for further manipulation. As a model study for introduction of the 1,3-diketone functionality, bicyclo[4.2.1]nonane-2,4-dione **43** was also prepared. Methylation of the penultimate intermediate **62** under conditions reported in isolation of the natural product did not give the tetramethyl ether **2** but a mixture of the trimethyl ethers **64** and **65**. With Me_3OBF_4 and Proton Sponge, the transformation to **2** was successfully achieved. The structure of the synthetic **2** was secured by the X-ray crystallographic structure analysis of the key compound **60**. However, the difference between the spectra of the synthetic **2** and those of the compound derived from the natural product suggests the structure of the latter is incorrect and requires revision.

Introduction

Mediterraneol B, isolated in 1986 from the brown alga *Cystoseira mediterranea*, inhibits the mitotic cell division in the fertilized urchin eggs (ED_{50} = 2 mg/mL) and exhibits antitumor activity against P388 leukemia (T/C = 128% at 32 mg/kg).[1] This diterpenoid and its closely related metabolite were isolated as a mixture and were unstable during open column chromatography, but successful separation was achieved by using methylation (MeI/K_2CO_3). On the basis of detailed spectroscopic analysis, the unique structure **2** was assigned to the tetramethylated derivative, and therefore, the structure **1** was proposed for the natural product. The central structural features are the bicyclo[4.2.1]nonane framework with three continuous quaternary carbon centers and the unusual displacement of the methyl group from C11 of the regular terpenoid precursor to C14 in the cyclic product. Recently the same diterpenoid was also isolated from the different alga, *Cystoseira stricta* and *Cystoseira tamariscifolia*.[2,3] So far total synthesis of the novel natural product has not been achieved yet.[4] Herein we disclose an unambiguous, fully stereocontrolled synthesis of the compound **2** which demonstrates that mediterraneol B cannot be constituted as originally proposed.

As an extension of our studies on development of new synthetic method by using selective skeletal transformation,[5] we have reported a new method for efficient construction of bicyclo[4.2.1]nonanes by acid-catalyzed



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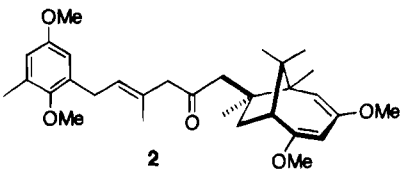

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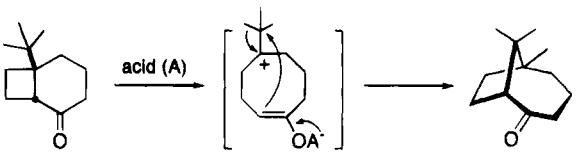
rearrangement of 6-4 fused ring system.[6] For example, reaction of the ketone **3** having a *tert*-butyl group at the bridgehead position gave trimethylbicyclononanone **5** in high yield via the cyclooctenyl cation **4**. Since the ketone



3 **4** **5**

5 has the same framework as the above diterpenoid and involves two continuous quaternary carbon centers, *i.e.*, C14 and C15,[7] we envisaged that this technology could be applied to the efficient synthesis of the compound **2** proposed for tetramethylmediterraneol B. Our convergent synthetic plan derived from a retrosynthetic analysis was designed to assemble two segments, the hydro-

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(1) Francisco, C.; Banaigs, B.; Teste, T.; Cave, A. *J. Org. Chem.* **1986**, *51*, 1115.

(2) Piovetti, L.; Deffo, P.; Valls, R.; Peiffer, G. *J. Chromatogr.* **1991**, *588*, 99.

(3) Valls, R.; Piovetti, L.; Banaigs, B.; Praud, A. *Phytochemistry* **1993**, *32*, 961.

(4) One synthetic study was, to our knowledge, presented: Nagaoka, H.; Okamura, T.; Yamada, Y. Abstract of papers, 111th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1991, p 70.

(5) Kakiuchi, K.; Fukunaga, K.; Jimbo, M.; Yamaguchi, B.; Tobe, Y. *J. Org. Chem.* **1992**, *57*, 1021 and references cited therein.

(6) Kakiuchi, K.; Fukunaga, K.; Matsuo, F.; Ohnishi, Y.; Tobe, Y. *J. Org. Chem.* **1991**, *56*, 6742.

(7) The mediterraneol B numbering system, as depicted for **1**, will be used throughout this paper.

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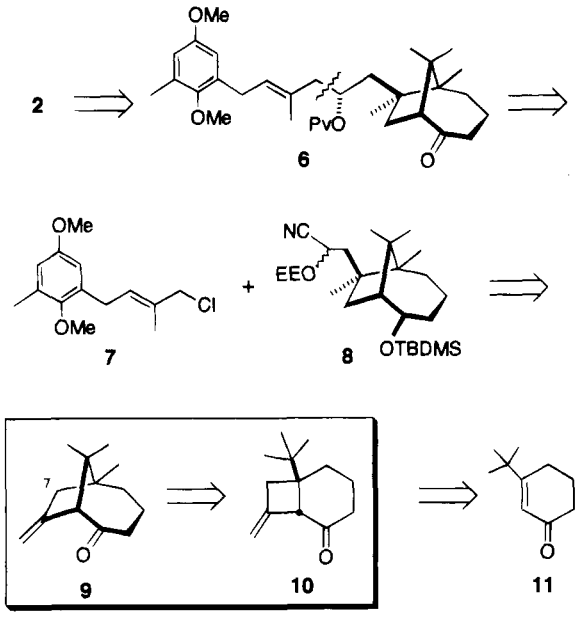
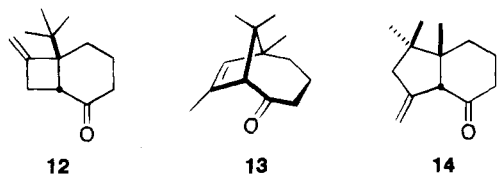
Scheme 1



quinone side chain **7** and the bicyclo[4.2.1]nonane moiety **8** (Scheme 1). At the last stage, introduction of the 1,3-diketone functionality to the intermediate **6** should give the target molecule **2**. The methylated hydroquinone segment **7** should be prepared easily according to the reported method.[8] The key component **8** would be derived from bicyclo[4.2.1] ketone **9** having a clue for introduction of C7 alkyl substituents. The cornerstone of the synthesis is the acid-catalyzed rearrangement of the *exo*-methylene ketone **10** to the ketone **9**. The ketone **10** would be available by photocycloaddition of 3-*tert*-butylcyclohex-2-en-1-one (**11**) to allene.

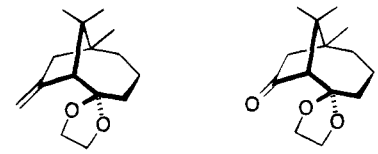
Results and Discussion

Synthesis of Bicyclic Segment 8. Irradiation of the enone **11**[9] with allene in CH_2Cl_2 at −78 °C gave the head to head adduct **10** in 91% yield together with the head to tail adduct **12** in 3% yield. The regiochemistry was easily ascertained by their NMR spectra. The adduct **10** showed a signal at δ 3.51, attributed to the methine proton of the bridgehead position, whereas for **12** no signal was detected around 3.5 ppm. In the ^{13}C NMR spectra, the signal of the bridgehead tertiary carbon (δ 55.5) of **10** appeared at lower field than that (δ 44.1) of **12**, while the signal of the bridgehead quaternary carbon (δ 44.8) of **10** was observed at higher field than that (δ 59.0) of **12**, due to the *exo*-methylene moiety.



Now the stage was set for the acid-catalyzed rearrangement of ketone **10**, the pivotal step in this synthesis. Fétizon and co-workers reported that acid-catalyzed rearrangement of some cyclohexenone−allene photocycloadducts did not proceed through the cyclooctenyl cation such as **4** but via cleavage of the external cyclobutane bond or 1,2-migration of the cyclobutane bond (Cargill rearrangement),[10] depending on the acid employed.[11] To obtain the desired compound **9**, therefore, we investigated acid-catalyzed rearrangement of **10** using various acid, TsOH, H_2SO_4, TfOH, BF_3·OEt_2, $FeCl_3$, $AlCl_3$, $TiCl_4$, and BCl_3. Among them, $TiCl_4$ and BCl_3 were most useful for this transformation.[12] Thus with 2 equiv of $TiCl_4$ in CH_2Cl_2 at rt, we obtained the ketone **9** in 60% yield along with the inner olefin product **13** in 4% yield. The structure of **9** was unambiguously determined by 2D ^{13}C-INADEQUATE spectrum. In the case of BCl_3 (3 equiv), the yield of ketone **9** was slightly higher (66%) but the 6-5 fused ketone **14** was produced in 11% yield as a byproduct.

With the ketone **9** in hand, we turned next to the chemical transformation to the segment **8** (Scheme 2). For this purpose, first, the carbonyl group of **9** was protected as a 1,3-dioxolane (ethylene glycol, (1*S*)-(+)-camphorsulfonic acid (CSA), trimethyl orthoformate, CH_2Cl_2, rt, 90%). Ozonolysis of the resulting acetal **15**, however, gave the corresponding ketone **16** in low yield (< 10%). Furthermore, reaction of **15** with OsO_4−$NaIO_4$

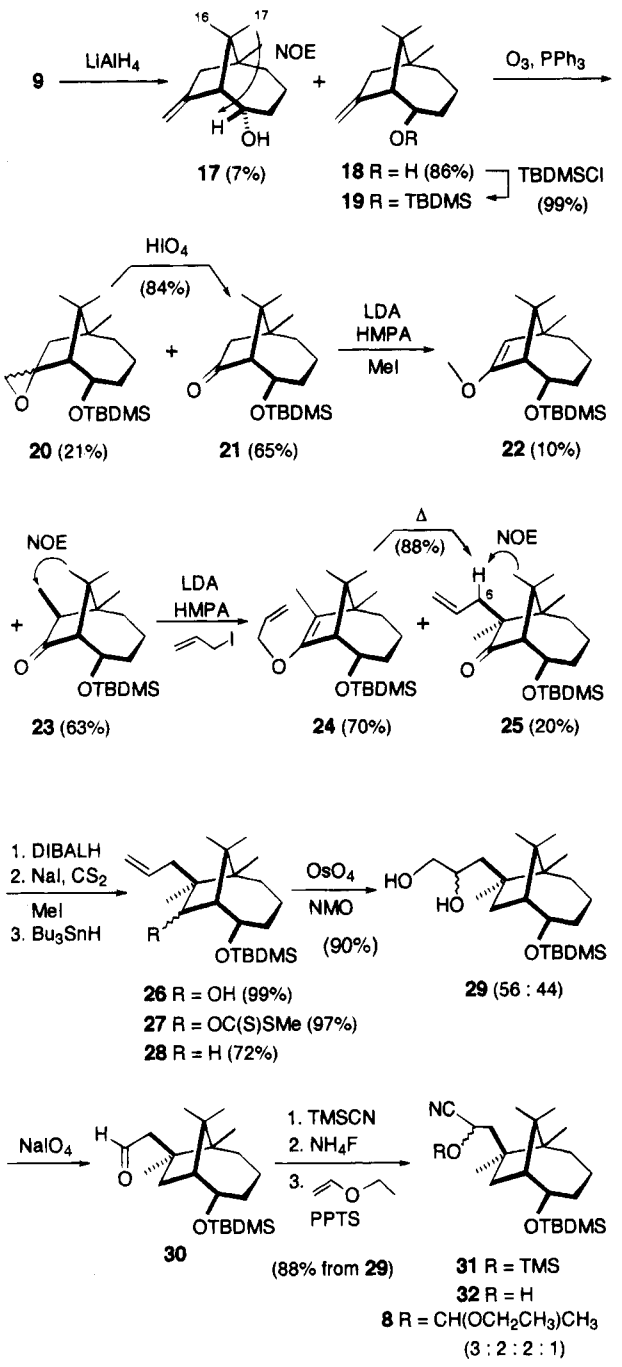


hardly proceeded where **15** was recovered. Since we could not obtain a large quantity of **16**, we employed a circuitous route. Thus reduction of **9** with $LiAlH_4$ in ether at −40 °C gave the β-alcohol **18** in 86% yield together with the α-alcohol **17** in 7% yield. The stereochemistry of the hydroxyl group was assigned on the basis of the NOE experiment where presaturation of the C17 methyl protons (δ 1.02) of **17** resulted in an NOE enhancement (3%) of C10-Hβ (δ 3.86). These results show that the hydride attacks the C10 carbonyl from the less hindered α-face predominantly. Protection of the hydroxyl group of the major alcohol **18** with TBDMSCl and imidazole in DMF gave the TBDMS ether **19** in 99% yield. Ozonolysis of **19** in MeOH in the presence of pyridine at ca. −60 °C followed by addition of PPh_3 afforded the ketone **21** in 65% yield along with the epoxide **20** in 21% yield which was converted to **21** in 84% yield by treatment with HIO_4 in THF−ether at 0 °C.[13]

Methylation of **21** with an excess amount of LDA (5 equiv), HMPA (15 equiv), and MeI (15 equiv) in THF at −78 °C gave the compound **23** in 63% yield as a single stereoisomer along with 25% of the starting ketone and 10% of the methyl enol ether **22** which was transformed to **21** in 96% yield by reaction with citric acid in MeOH. The assignment of the stereochemistry of C7-βMe of **23**

(8) Mori, K.; Uno, T. *Tetrahedron* **1989**, *45*, 1945.
(9) Piers, E.; Nagakura, I. *J. Org. Chem.* **1975**, *40*, 2694.
(10) Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond, D. M. *Acc. Chem. Res.* **1974**, *7*, 106.
(11) Duc, D. K. M.; Fétizon, M.; Hanna, I; Lazare, S. *Synthesis* **1981**, 139. Duc, D. K. M.; Fétizon, M.; Hanna, I.; Olesker, A. *J. Chem. Soc., Chem. Commum.* **1980**, 1209, and references cited therein.
(12) With other acids, bicyclo[4.3.0]nonanone derivatives were obtained mainly. Acid-catalyzed rearrangement of other methylene-bicyclo[4.2.0]octan-2-ones including the present results will be reported in due course.
(13) Paquette, L. A.; Fisher, J. W.; Browne, A. R.; Doecke, C. W. *J. Am. Chem. Soc.* **1985**, *107*, 686.

Scheme 2



was based on the NOE experiment where presaturation of the C16 methyl protons (δ 0.98) resulted in an NOE enhancement (15%) of the methyl protons (δ 1.20).[14] Similarly, treatment of the methyl ketone **23** with LDA (7.5 equiv) and allyl iodide (15 equiv) in THF–HMPA (3:1) at −78 °C then at rt gave the *C*-allylated ketone **25** in 20% yield and the allyl enol ether **24** in 70% yield. The latter was converted to the same ketone **25** in 88% yield through Claisen rearrangement by heating in *o*-xylene at 138 °C. The stereochemistry at C7 was assigned by the NOE experiment where presaturation of the C16 methyl protons (δ 1.20) resulted in an NOE enhancement (15%) of one of the allylic protons (δ 2.71) at C6[14] and was further confirmed by X-ray analysis of the more advanced key compound **60**. These results show that the severe steric hindrance around C7 interferes with the access of reagents and reactions take place at the relatively less hindered β-face. Therefore, the sequence of alkylations of **21** is crucial to the stereoselective synthesis of **25**. Thus three contiguous quaternary carbon centers were established.

Reduction of the C8 carbonyl of **25** to the methylene group was carried out by using Barton-McCombie reaction.[15] Treatment of **25** with DIBALH in ether at −78 °C gave the alcohol **26** in 99% yield as a single stereoisomer whose stereochemistry was not confirmed. Reaction of **26** with NaH and CS_2 in the presence of imidazole and HMPA in THF at 60 °C followed by addition of MeI produced the xantate **27** in 97% yield. Radical reduction of **27** using Bu_3SnH in the presence of AIBN in toluene at 60 °C afforded the compound **28** in 72% yield. Conversion of **28** to the cyanohydrin ethoxyethyl ether **8** was undertaken as follows. Oxidation of **28** with OsO_4 and 4-methylmorpholine *N*-oxide (NMO) in *t*-BuOH–THF–water at rt gave the diastereomeric diols **29** (56:44) in 90% yield. Oxidative cleavage of the mixture of **29** with $NaIO_4$ in THF–water afforded the aldehyde **30**.[16] Treatment[17] of **30** with TMSCN and ZnI_2 in CH_2Cl_2 at 0 °C followed by deprotection of the cyanohydrin TMS ether **31** with NH_4F in THF–water and subsequent reaction of the cyanohydrin **32** with ethyl vinyl ether and pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2 yielded the right wing **8** in 88% overall yield from **29** as a mixture of four diastereomers in a 3:2:2:1 ratio. The mixture was used for the next step without separation.

Synthesis of Hydroquinone Segment 7. The left wing **7** was readily synthesized from 1-bromo-2,5-dimethoxy-3-methylbenzene **33**[18] according to the reported method for the preparation of related compounds (Scheme 3).[8] Reaction of **33** with BuLi in ether at −50 °C followed by transmetalation with CuI and addition of allyl bromide gave the compound **34** in 75% yield. After one carbon contraction of the allyl group via the diol **35** (OsO_4, NMO, then $NaIO_4$) as described above, the Wittig reaction of the resulting aldehyde **36** with ethyl 2-(triphenylphosphoranylidene)propionate[19] in CH_2Cl_2 afforded a mixture of the α,β-unsaturated esters **37** and **38** in 4% and 88% overall yields from **35**. When the C20 methyl protons (δ 1.98) of **38** was irradiated, an NOE enhancement (5%) was observed in the C1 methylene protons (δ 3.52), indicating the *E* geometry of its double bond as depicted in **38**. The minor ester **37** also exhibited NOE (8%) between the C20 methyl (δ 1.96) and the C2 vinyl protons (δ 6.04), supporting the *Z* geometry of its double bond. Reduction of the ester **38** with DIBALH in CH_2Cl_2 at −78 °C followed by treatment of the alcohol

(14) Assignments are based on H–H decoupling or H–H COSY, C–H COSY, long-range C–H COSY, and NOE difference spectra, and on comparison with compounds whose assignments were established. For detailed assignment, see Tables S1 and S2 of the supplementary material listing ^{13}C NMR and ^{1}H NMR data for synthetic intermediates and model compounds.

(15) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1971**, 1574.

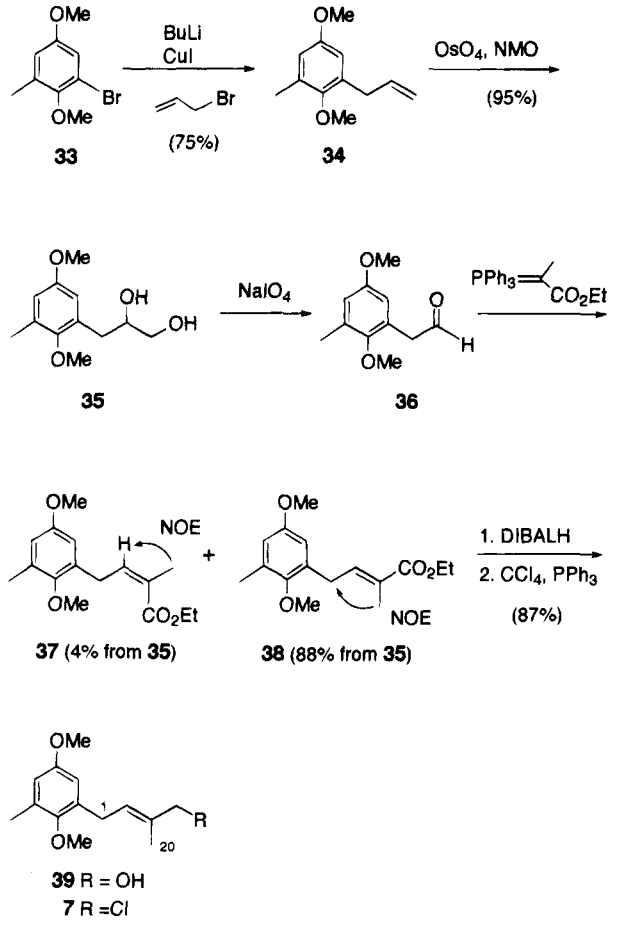
(16) One-step transformation of **28** to **30** by ozonolysis or Lemieux–Jonhson oxidation (OsO_4, $NaIO_4$) gave **30** in low yields (ca. 10% or 40%, respectively). On standing at rt for a day, the aldehyde **30** decomposed to give a complex mixture of products.

(17) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929. Greenlee, W. J., Hanguaer, D. G. *Tetrahedron Lett.* **1983**, *24*, 4559.

(18) Raistrick, H; Robinson, R.; White, D. E. *Biochem. J.* **1936**, *30*, 1303.

(19) Isler, O.; Gutmann, H.; Montavon, M.; Rüegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957**, *139*, 1242. Hashimoto, M.; Harigaya, H.; Yanagiya, M. ; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299.

Scheme 3



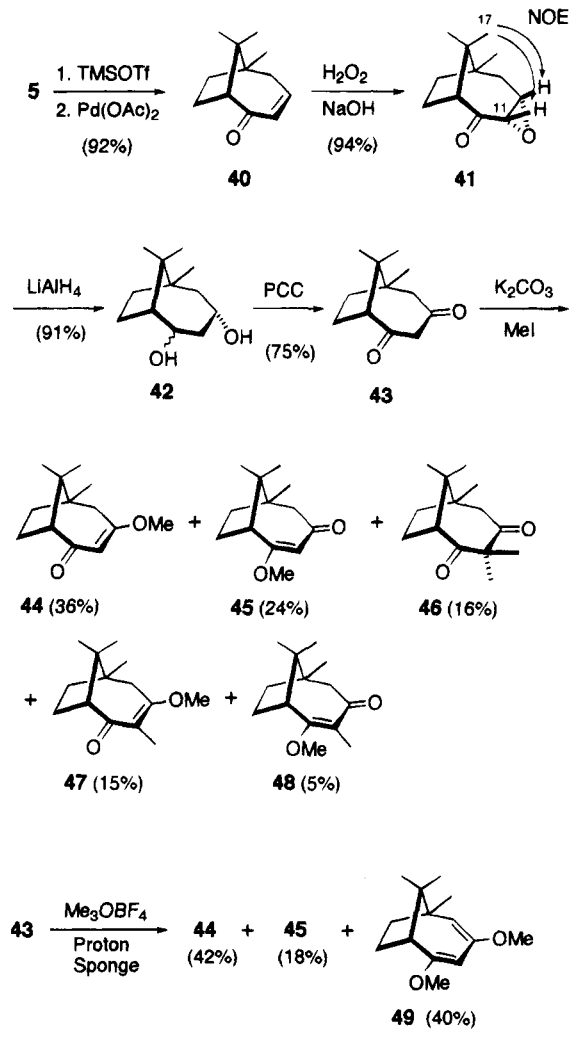
39 with CCl_4 and PPh_3 at 85 °C gave the segment **7** in 87% overall yield.

Model Study for Construction of 1,3-Diketone Functionality. As a model study, introduction of the 1,3-diketone functionality to the bicyclononanone **5** was undertaken (Scheme 4). We planned to pursue this transformation through reduction of an epoxy ketone followed by oxidation of the resulting 1,3-diol. Reaction of **5** with TMSOTf and Et_3N in CCl_4 followed by treatment of the silyl enol ether with $Pd(OAc)_2$ and Na_2CO_3 in MeCN gave the enone **40** in 94% overall yield.[20] Epoxidation of **40** with 30% H_2O_2 and aqueous NaOH in MeOH at rt afforded the epoxy ketone **41** in 94% yield as a single isomer. The stereochemistry of the α-epoxide ring was ascertained by the NOE experiment where irradiation of the C17 methyl protons (δ 0.77) caused NOE enhancements (4.5% and 5%) of the C11 and C12 β-protons (δ 3.28 and 3.34).[14] Reduction of **41** with $LiAlH_4$ in ether gave the single diol **42** in 91% yield where the stereochemistry of C10 was not confirmed. PCC oxidation of **42** in the presence of NaOAc and molecular sieves, 4A (MS4A), in CH_2Cl_2 produced the 1,3-diketone **43** in 75% yield.

Methylation of the diketone **43** with MeI and K_2CO_3 under the conditions reported in isolation of natural products,[1] however, did not give the dimethyl ether **49**. A mixture of monomethylated ketones **44** and **45** and *C*-methylated ketones **46**, **47**, and **48** was obtained in 36%, 24%, 16%, 15%, and 5% yields, respectively.[21] After examination of several methods, we found that the

(20) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

Scheme 4



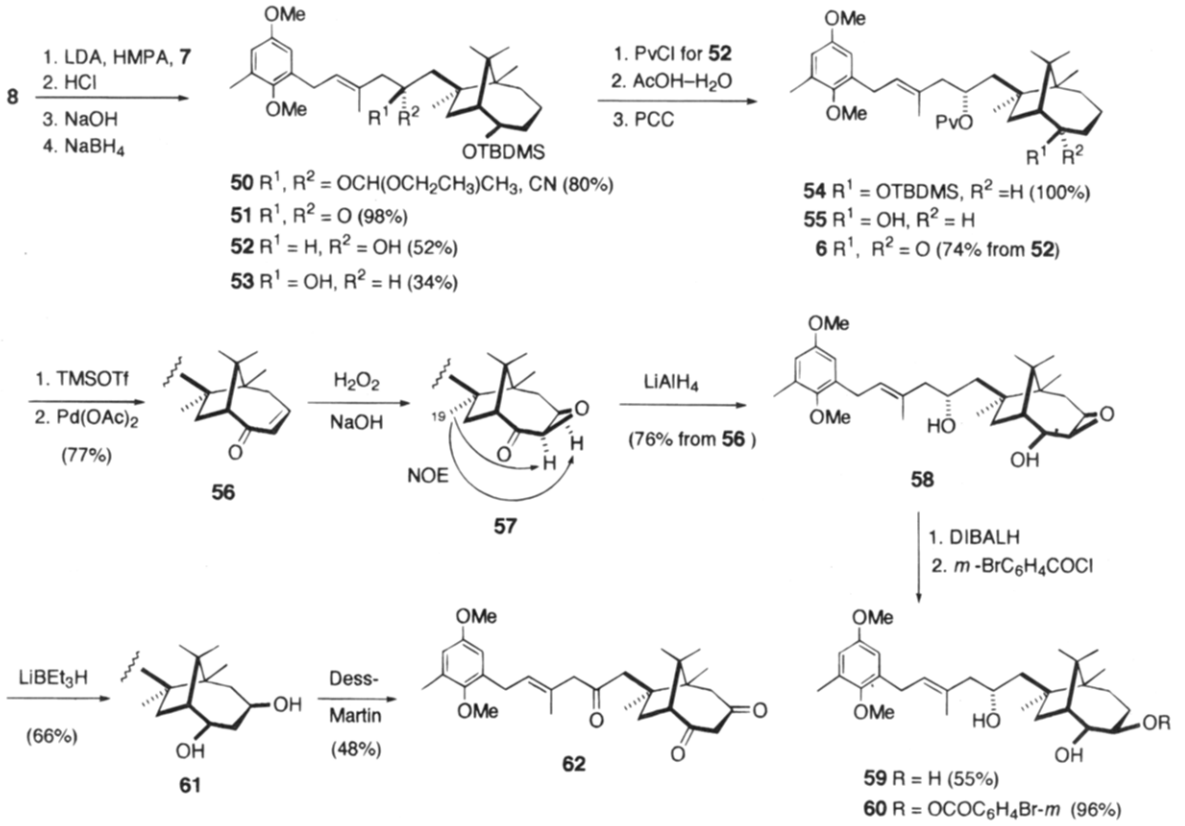
reaction[22] of **43** with Me_3OBF_4 and 1,8-bis(dimethylamino)naphthalene (Proton Sponge, Aldrich) at rt gave the desired compound **49** in 40% yield along with **44** and **45** in 42% and 18% yields. We noted that the dimethyl ether **49** was highly sensitive toward acid and underwent demethylation easily to a mixture of the monomethyl ethers **44** and **45** during the acidic workup.

Completion of Synthesis of Proposed Structure 2 for Tetramethylmediterraneol B. For the completion of the synthesis, coupling between the two segments **7** and **8** was undertaken (Scheme 5). Deprotonation of **8** with LDA and HMPA in THF at −45 °C followed by addition of **7** gave the coupling product **50**, having the carbon framework of the natural product, in 80% yield as a mixture of four possible diastereomers. Before introduction of the 1,3-diketone moiety to the bicyclic skeleton, the functionality of C5 was temporarily changed to a pivaloyl ester to avoid the migration of the nonconjugated double bond during the remaining course of the synthesis. Advantageously, reduction followed by oxidation, which are essential steps for the buildup of the 1,3-diketone moiety as described above, should reproduce the

(21) The regiochemistry of the monomethylated products **44** (δ 2.67 for the C9 proton), **45** (δ 2.49), **64** (δ 2.64), and **65** (δ around 2.5) was assigned based on general tendency that methine proton located at α-position of carbonyl group appears at lower field than allylic methine proton.

(22) Diem, M. J.; Burow, D. F.; Fry, J. L. *J. Org. Chem.* **1977**, *42*, 1801.

Scheme 5



carbonyl group at C5 from the pivaloyl-protected hydroxyl without any extra steps. Thus selective removal of the ethoxyethyl protecting group of **50** with HCl–$CHCl_3$ followed by treatment with NaOH in aqueous ether gave the single ketone **51** in 98% overall yield. Reduction of **51** with $NaBH_4$ in MeOH yielded a separable mixture of the alcohols **52** and **53** in 52% and 34% yields, respectively. To avoid the complication in the later synthesis, the major diastereomer **52** was used for the remaining steps.[23] Protection of the hydroxyl group in **52** with pivaloyl chloride (PvCl) and DMAP in pyridine gave the ester **54**. Although the stereochemistry of C5 was not determined at this stage, the X-ray analysis of the more advanced intermediate **60** revealed it as shown in **54**. Deprotection of the TBDMS group in **54** in AcOH–THF–water at 50 °C followed by PCC oxidation of the alcohol **55** as described above gave the ketone **6** in 74% overall yield from **52**.

With the ketone **6** in hand, we set out to introduce the 1,3-diketone functionality as the final stage. Based on the model study, the ketone **6** was converted to the enone **56** in 77% overall yield in two steps. However, epoxidation of **56** under conditions similar to those for the model compound **40** did not proceed. When the reaction was carried out at 30 °C for 4 days, the epoxide **57** was obtained as a single isomer. In contrast to the model compound **41**, the β-configuration of the epoxy ring in **57** was assigned by the NOE experiment. Irradiation of the C19 methyl protons (δ 1.15) showed NOE enhancements (2% and 13%) of the C12 and C13 α-protons (δ 3.17 and 3.25).[14] In the case of **40** without the C19 methyl group, the nucleophile (OOH^-) attacks C12 from the less hindered α-face due to the steric hindrance of the C17 methyl group. The reduced reactivity of **56** toward the nucleophile is also rationalized from the inspection of MM2-calculated structures of **40** and the model system **63** having methyl and allyl groups at C7 (Figure 1).[24] In the case of **63**, both sides of C12 are hindered by the C17 and C19 methyl groups. Since the C17 methyl group is located at a position further from the C12 methyl than the C19 methyl, the reagent would approach selectively from the β-face to give the β-epoxide **66**. Indeed, the enone **63**[25] showed the reactivity similar to that of **56** to give **66**.

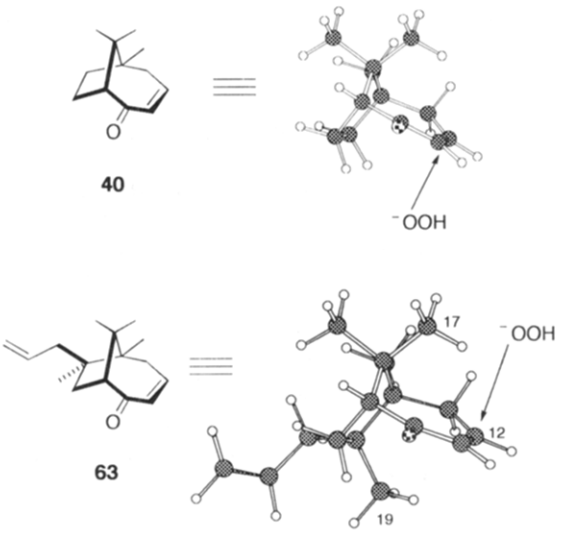


Figure 1. The most stable conformers of **40** and **63**.

(23) Since preliminary epoxidation of the mixture of the enone **56** and the diasteromer of **56** derived from **53** gave a complex mixture of products involving the epoxide **57**, we used the major diasteromer **52** for the remaining steps.

(24) Allinger, N. L. *QCPE No. MM2 (85).*

(25) This compound was obtained from the intermediate **28** according to the same procedure as shown in Scheme 5, see the Experimental Section.

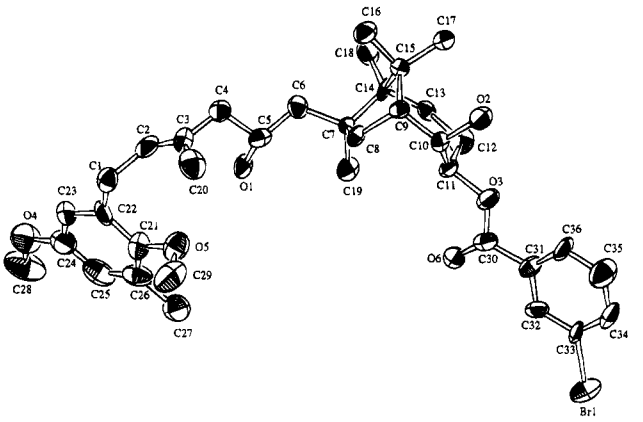


Figure 2. Molecular structure of *m*-bromobenzoate **60**.

Reduction of the epoxide **57** with $LiAlH_4$ in ether at 0 °C afforded the diol **58** in 76% overall yield from the enone **56**. However, the epoxy ring was kept untouched under these conditions. Further reaction of **57** with $LiAlH_4$ in ether or THF at higher temperature gave the complex results. Red-Al (Aldrich), a solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene, known as the regioselective reducing reagent for α,β-epoxy alcohols to 1,3-diols,[26] was also unavailing for the reduction of **58**. Treatment of **58** with DIBALH in CH_2Cl_2 at −78 °C then at rt yielded a triol in 55% yield, which was revealed not to be a 1,3-diol but 1,2-diol **59** by the X-ray structural analysis of *m*-bromobenzoate **60** (*m*-BrC_6H_4-COCl (1 equiv), pyridine, rt, 96%) (Figure 2). This result also established that **60** and therefore the intermediates leading to **60** have indeed bicyclo[4.2.1]nonane framework and the required stereochemistry of the stereogenic centers.

Finally, the epoxide **58** was reduced by $LiBEt_3H$ in THF to give the desired 1,3-diol **61**. In this case the reaction hardly proceeded at rt and was completed in 4−5 days at 65 °C. Although suitable crystals for X-ray analysis were not obtained from **61**, this compound was fully characterized by the H−H COSY, C−H COSY, long-range C−H COSY, and NOE experiments. PCC oxidation of the triol **61**, however, gave complex results. PDC and Swern oxidations were not effective for this transformation. In the event, treatment of **61** with the Dess−Martin reagent[27] in CH_2Cl_2 at rt afforded the triketone **62** in 48% yield, which is regarded as the dimethylated derivative of the natural product.

Curiously methylation of **62** with MeI−K_2CO_3 under the conditions reported in isolation of natural products[1] did not give the tetramethyl ether **2**. The monomethyl ethers **64** and **65**[21] were obtained in 33% and 20% yields, respectively, along with a trace amount of *C*-methylated compound, like the model study as described above (Scheme 6). Reaction of **62** with Me_3OBF_4 and Proton Sponge at rt furnished also a mixture of **64** and **65** which were subjected to the same reaction at 40 °C to give **2** as a colorless oil,[28] the compound proposed for tetramethylmediterraneol B. This compound was also unstable toward acid, affording the monomethyl ethers **64** and **65** as was the model compound **49**. However, the NMR data

Scheme 6

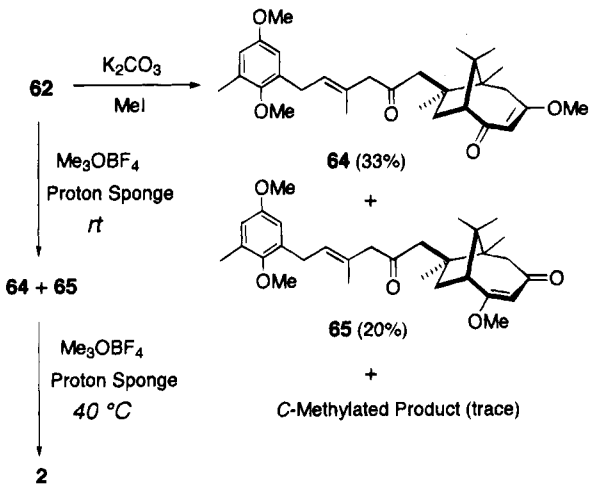


Table 1. ^1H NMR and ^{13}C NMR Data of Synthetic and Natural Product 2 in $CDCl_3$

	^1H NMR		^{13}C NMR	
C no.	synthetic **2**	natural **2**[a]	synthetic **2**	natural **2**[a]
1	3.39	3.34	28.6	28.6
2	5.41	5.38	128.0	127.1
3			130.3	130.4
4	3.04	3.09	56.0	39.4
5			208.6	210.3
6	2.70, 2.48	2.85 (AB)	53.3	48.4
7			49.7	47.8
8	2.44, 1.95	2.37, 1.89	48.0	35.6
9	2.13	3.13	55.0	38.4
10			151.9	158.8
11	4.70	5.99[c]	94.7	90.7
12			166.3	160.1
13	3.97	5.95[c]	103.8	92.9
14			51.5	53.0[b]
15			41.5	52.4[b]
16	1.13[d]	1.23	27.2	26.5
17	1.06	1.04	22.4	25.6
18	0.90	1.28	21.9	22.8
19	1.10[d]	1.08	27.0	21.9
20	1.73	1.74	16.5[e]	16.3
1′			150.4	154.0
2′			134.7	134.8[f]
3′	6.57	6.54	112.8	113.2[g]
4′			155.6	155.2
5′	6.57	6.54	113.9	114.0[g]
6′			132.6	131.2[f]
7′	2.29	2.26	16.4[e]	16.0
10-OMe	3.51[h]	3.75[i]	54.9[j]	56.4[k]
12-OMe	3.48[h]	3.74[i]	54.2[j]	55.4[k]
1′-OMe	3.69	3.65[l]	60.5	55.4[m]
4′-OMe	3.76	3.75[l]	55.4	55.3[m]

[a] Reference 1. [b−m] Assignments may be reversed.

of the synthetic **2** are different from those reported for the tetramethylated derivative of mediterraneol B derived from natural resources. There are notable discrepancies between the NMR spectra of the synthetic compound and those reported for tetramethylmediterraneol B,[1] especially for C4, C8, bridgehead carbon and proton (C9 and H9), vinyl carbon and protons of bis-enol ether moiety (C13, H11, and H13), C15, and the methoxy carbon attached to C1′ as shown in Table 1. The results of NOE experiments of the synthetic **2** are shown in Figure 3, where C_6D_6 was used instead of $CDCl_3$ to avoid the decomposition of **2** to **64** and **65** (Figure 3). Judging from the spectral data of the synthetic **2** and those of the intermediate **62**, the possibility that skeletal transformations or unusual reactions have occurred during the conversion **61** to **2** is improbable.

(26) Finn, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719. Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*. 4081.
(27) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(28) It was reported that the tetramethylmediterraneol B derived from the natural product was obtained as white foam.[1]

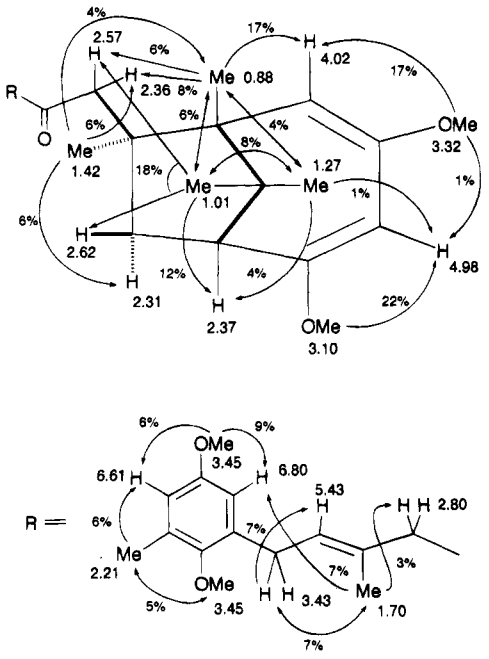
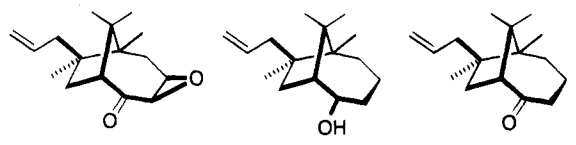


Figure 3. NOE for the synthetic compound **2** in C_6D_6.

In conclusion, the compound **2** proposed for tetramethylmediterraneol B was synthesized in a stereocontrolled manner by utilizing the acid-catalyzed rearrangement for construction of the bicyclo[4.2.1]nonane framework. At present, we are unable to propose rational alternative structures for natural tetramethylmediterraneol which are consistent with the degradation study, NOE experiments, and long-range C–H COSY of the related compound performed by Francisco. On the basis of the present synthetic studies, the assignment of the structures of mediterraneol B and its tetramethylated derivative as **1** and **2** is concluded to be erroneous and has to be revised.

Experimental Section

All melting points were uncorrected. Instruments for the measurement of spectra and technique of chromatography were used in the previous work.[5] All dry solvents were purified before use by standard procedures.



66 **67** **68**

Synthesis of Segment 8. (1*R,6*R**)-6-*tert*-Butyl-8-methylenebicyclo[4.2.0]octan-2-one (10) and (1*R**,6*R**)-6-*tert*-Butyl-7-methylenebicyclo[4.2.0]octan-2-one (12).** A solution of 3-*tert*-butylcyclohex-2-en-1-one (**11**)[9] (6.88 g, 45.3 mmol) and allene (35 mL) in dry CH_2Cl_2 (240 mL) was irradiated at −78 °C for 4.5 h in a Pyrex vessel with a 500-W high-pressure mercury lamp. Allene and the solvent were evaporated, and the residue was chromatographed on SiO_2 (elution with ether/petroleum ether, 3:97) to give **10** (7.89 g, 91%) and **12** (0.28 g, 3%). **10**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92–4.88 (m, 2H), 3.51 (dd, J = 6.3, 3.3 Hz, 1H), 2.93 (dt, J = 16.9, 2.6 Hz, 1H), 2.55 (m 1H), 2.38 (ddd, J = 16.9, 5.9, 2.6 Hz, 1H), 2.17–2.00 (m, 2H), 1.88 (m, 1H), 1.73–1.61 (m, 2H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4 (s), 141.0 (s), 108.9 (t), 55.5 (d), 44.8 (s), 38.5 (t), 36.0 (t), 34.7 (s), 29.9 (t), 24.7 (q, 3C), 18.8 (t); IR (neat) 1700, 1670, 1370, 880 cm^{-1}; MS m/e (rel intensity) 192 (M^+, 10), 177 (100), 149 (76), 121 (83), 57 (75); HRMS calcd for $C_{13}H_{20}O$ 192.1514, found 192.1523. **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96–4.92 (m, 2H), 2.97–2.84 (m, 2H), 2.60–2.43 (m, 2H), 2.14–1.85 (m, 3H), 1.76 (m, 1H), 1.50 (dt, J = 13.2, 4.0 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9 (s), 152.0 (s), 107.4 (t), 59.0 (s), 44.1 (d), 38.8 (t), 34.9 (s), 32.9 (t), 28.8 (t), 25.0 (q, 3C), 19.4 (t); IR (neat) 1700, 1665, 1370, 880 cm^{-1}; MS m/e (rel intensity) 192 (M^+, trace), 136 (87), 108 (67), 57 (100); HRMS calcd for $C_{13}H_{20}O$ 192.1514, found 192.1513.

(1*R,6*S**)-8-Methylene-6,9,9-trimethylbicyclo[4.2.1]-nonan-2-one (9), (1*R**,6*S**)-6,8,9,9-Tetramethylbicyclo-[4.2.1]non-7-en-2-one (13), and (1*R**,6*R**)-9-Methylene-6,7,7-trimethylbicyclo[4.3.0]nonan-2-one (14).** To a solution of **10** (14.9 g, 77.3 mmol) in dry CH_2Cl_2 (300 mL) was added $TiCl_4$ (18 mL, 145 mmol) at rt. The mixture was stirred at rt for 1.5 h and poured into saturated aqueous $NaHCO_3$. The white precipitate was filtered off through Cerite, and the filtrate was extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography on SiO_2 (elution with ether/petroleum ether, 2:98) gave **9** (8.94 g, 60%) and **13** (0.75 g, 5%). **9**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (m, 1H), 5.00 (m, 1H), 3.16 (s, 1H), 2.59–2.50 (m, 2H), 2.44 (m, 1H), 2.34 (ddd, J = 19.5, 13.6, 4.4 Hz, 1H), 2.00 (m, 1H), 1.82 (m, 1H), 1.60 (m, 1H), 1.48 (m, 1H), 1.01 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0 (s), 147.6 (s), 110.2 (t), 73.2 (d), 45.9 (s), 45.2 (s), 43.9 (t), 41.5 (t), 38.8 (t), 28.2 (q), 23.2 (q), 20.2 (t), 19.0 (q); IR (neat) 1690, 1640, 880, 780 cm^{-1}; MS m/e (rel intensity) 192 (M^+, 61), 149 (69), 121 (100); HRMS calcd for $C_{13}H_{20}O$ 192.1514, found 192.1517. **13**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 1H), 2.74 (s, 1H), 2.57–2.41 (m, 2H), 1.71 (s, 3H), 1.60–1.43 (m, 4H), 1.04 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2 (s), 136.6 (d), 135.4 (s), 77.4 (d), 52.6 (s), 46.5 (s), 43.9 (t), 38.0 (t), 28.7 (q), 21.8 (t), 20.7 (q), 19.0 (q), 15.6 (q); IR (neat) 1685, 1650, 840 cm^{-1}; MS m/e (rel intensity) 192 (M^+, 46), 177 (100), 149 (82), 121 (96); HRMS calcd for $C_{13}H_{20}O$ 192.1514, found 192.1484. To a solution of **10** (270 mg, 1.41 mmol) in dry CH_2Cl_2 (4 mL) was added 1 M BCl_3 in dry CH_2Cl_2 (4.23 mL, 4.23 mmol) under N_2 at 0 °C, and the mixture was stirred at rt for 1 h. Ice–water was added, and the mixture was extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/petroleum ether, 3:97) gave **9** (180 mg, 66%) and **14** (30 mg, 11%). Similar reaction of **10** (5.87 g) with BCl_3 gave **9** (3.33 g, 57%) and **14** (0.65 g, 11%). **14**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (m, 1H), 4.74 (m, 1H), 3.13 (s, 1H), 2.63 (dd, J = 17.1, 1.5 Hz, 1H), 2.41 (dt, J = 6.3, 14.2 Hz, 1H), 2.22 (d, J = 17.1 Hz, 1H), 2.15 (m, 1H), 1.94 (m, 1H), 1.76 (tq, J = 3.6, 13.6 Hz, 1H), 1.58 (dt, J = 3.7, 13.6 Hz, 1H), 1.41 (m, 1H), 0.95 (s, 3H), 0.93 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1 (s), 147.8 (s), 108.4 (t), 64.5 (d), 51.0 (s), 46.0 (t), 42.9 (s), 37.7 (t), 29.8 (t), 24.7 (q), 22.5 (t), 21.5 (q), 18.0 (q); IR (neat) 1700, 1640, 890 cm^{-1}; MS m/e (rel intensity) 192 (M^+, 21), 177 (100), 149 (63), 121 (55); HRMS calcd for $C_{13}H_{20}O$ 192.1514, found 192.1491.

(1*R,6*S**)-2,2-(Ethylenedioxy)-8-methylene-6,9,9-trimethylbicyclo[4.2.1]nonane (15).** A solution of **9** (105 mg, 0.57 mmol), ethylene glycol (1.50 mL, 26.9 mmol), trimethyl orthoformate (0.90 mL, 8.22 mmol), and (*S*)-(+)-CSA monohydrate (41 mg, 0.18 mmol) in dry CH_2Cl_2 (4 mL) was stirred at rt for 4.5 h. Cold aqueous KOH was added, and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography on SiO_2 (elution with ether/petroleum ether, 2:98) gave **15** (116 mg, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (m, 1H), 5.04 (m, 1H), 4.03–3.94 (m, 2H), 3.89–3.80 (m, 2H), 2.43–2.23 (m, 4H, containing s at 2.29), 1.92 (m, 1H), 1.68–1.34 (m, 4H), 1.12 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0 (s), 114.8 (s), 112.4 (t), 64.2 (t), 63.8 (t), 62.6 (d), 45.1 (s), 44.8 (s), 43.9 (t), 40.8 (t), 38.6 (t), 29.6 (q), 23.4 (q), 20.4 (t), 19.6 (q); IR (neat) 1640, 1100, 880 cm^{-1}; MS

m/e (rel intensity) 236 (M^+, 13), 113 (69), 99 (100), 86 (64); HRMS calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1747.

(1*S,6*S**)-2,2-(Ethylenedioxy)-6,9,9-trimethylbicyclo[4.2.1]nonan-8-one (16).** A solution of **15** (50 mg, 0.21 mmol) in dry MeOH (10 mL) was ozonized at −78 °C until the blue color of excess ozone was observed. The excess ozone was purged by bubbling argon, and PPh_3 (115 mg, 0.42 mmol) was added. The mixture was warmed up to rt. Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/petroleum ether, 25:75) gave a mixture of unidentified compounds (35 mg) and **16** (4 mg, 8%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (m, 1H), 3.98 (m, 1H), 3.89−3.78 (m, 2H), 2.31 (d, *J* = 19.0 Hz, 1H), 2.19 (d, *J* = 19.0 Hz, 1H), 2.11 (s, 1H), 2.04 (ddd, *J* = 15.1, 13.7, 2.0 Hz, 1H), 1.91 (m, 1H), 1.83 (m, 1H), 1.66 (m, 1H), 1.48 (ddd, *J* = 14.7, 5.4, 2.4 Hz, 1H), 1.35 (m, 1H), 1.25 (s, 3H), 1.04 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1 (s), 111.2 (s), 67.1 (d), 64.1 (t), 64.0 (t), 49.1 (t), 43.0 (s), 42.8 (s), 40.2 (t), 38.5 (t), 29.5 (q), 22.8 (q), 20.5 (t), 18.9 (q); IR (neat) 1730, 1100, 1080, 940 cm^{-1}; MS *m/e* (rel intensity) 238 (M^+, 12), 99 (100), 86 (44); HRMS calcd for $C_{14}H_{22}O_3$ 238.1569, found 236.1593.

(1*R,2*S**,6*S**)- and (1*R**,2*R**,6*S**)-8-Methylene-6,9,9-trimethylbicyclo[4.2.1]nonan-2-ols (17 and 18).** To a mixture of $LiAlH_4$ (280 mg, 7.38 mmol) in dry ether (50 mL) was added a solution of **9** (1.78 g, 9.23 mmol) in dry ether (20 mL) dropwise at −40 °C. The mixture was stirred at −40 °C for 1 h. Ice−water was added carefully, and then 5% HCl was added. The mixture was extracted with ether, and the combined extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography on SiO_2 (elution with ether/petroleum ether, 10:90) gave **17** (0.14 g, 7%) and **18** (1.53 g, 86%). **17**: white solid, mp 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02−4.98 (m, 2H), 3.86 (dd, *J* = 11.2, 5.4 Hz, 1H), 2.44−2.40 (m, 2H), 2.30 (m, 1H), 2.04 (br s, 1H), 1.88 (m, 1H), 1.70−1.37 (m, 5H), 1.02 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0 (s), 108.4 (t), 70.4 (d), 63.0 (d), 45.9 (t), 45.2 (s), 43.9 (s), 40.7 (t), 34.5 (t), 29.5 (q), 25.1 (q), 20.9 (t), 18.3 (q); IR (KBr) 3300, 1640, 1020, 1000, 880 cm^{-1}; MS *m/e* (rel intensity) 194 (M^+, 7), 179 (56), 123 (100); HRMS calcd for $C_{13}H_{22}O$ 194.1670, found 194.1669. **18**: waxy white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (m, 2H), 4.02 (td, *J* = 8.8, 2.4 Hz, 1H), 2.45−2.35 (m, 2H), 2.20−2.13 (m, 2H), 1.73−1.44 (m, 5H), 1.38 (m, 1H), 1.18 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (s), 107.6 (t), 79.2 (d), 63.3 (d), 45.8 (s), 44.9 (s), 43.3 (t), 41.0 (t), 35.3 (t), 30.0 (q), 23.2 (q), 21.0 (t), 18.9 (q); IR (KBr) 3350, 1640, 1010, 880, 870 cm^{-1}; MS *m/e* (rel intensity) 194 (M^+, 17), 179 (58), 123 (100); HRMS calcd for $C_{13}H_{22}O$ 194.1670, found 194.1672.

(1*R,2*R**,6*S**)-2-(*tert*-Butyldimethylsiloxy)-8-methylene-6,9,9-trimethylbicyclo[4.2.1]nonane (19).** To a solution of **18** (6.52 g, 33.6 mmol) and imidazole (11.5 g, 168 mmol) in dry DMF (120 mL) was added TBDMSCl (6.08 g, 40.3 mmol) portionwise at rt under N_2. The mixture was stirred at rt for 46 h, and ice−water was added. The mixture was extracted with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography on SiO_2 (Merck-40, elution with petroleum ether) gave **19** (10.3 g, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (m, 1H), 4.88 (m, 1H), 3.96 (td, *J* = 8.8, 2.9 Hz, 1H), 2.39−2.32 (m, 2H), 2.13 (dd, *J* = 17.1, 1.5 Hz, 1H), 1.98 (m, 1H), 1.72−1.58 (m, 2H), 1.47−1.39 (m, 2H), 1.32 (m, 1H), 1.13 (s, 3H), 0.89 (s, 9H), 0.87 (s, 3H), 0.86 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (s), 106.9 (t), 79.0 (d), 63.6 (d), 45.8 (s), 44.9 (s), 43.6 (t), 41.1 (t), 35.9 (t), 30.2 (q), 25.8 (q, 3C), 23.3 (q), 21.2 (t), 19.0 (q), 18.0 (s), −4.6 (q), −4.8 (q); IR (neat) 1640, 1250, 1070, 830, 770 cm^{-1}; MS *m/e* (rel intensity) 307 (M^+ − 1, trace), 251 (83), 75 (100); HRMS calcd for $C_{19}H_{36}OSi$ 308.2535, found 308.2582.

(1*S,5*R**,6*R**)-5-(*tert*-Butyldimethylsiloxy)-1,9,9-trimethylspiro[bicyclo[4.2.1]nonane-7,2′-oxirane] (20) and (1*R**,2*R**,6*S**)-2-(*tert*-Butyldimethylsiloxy)-6,9,9-trimethylbicyclo[4.2.1]nonan-8-one (21).** Ozonolysis of **19** (2.56 g, 8.28 mmol and 5.13 g, 16.6 mmol) as described for the preparation of **16** at −60 to −70 °C gave **20** (1.73 g, 21%) and **21** (4.60 g, 60%) after column chromatography on SiO_2 (elution with ether/petroleum ether, 0.5:99.5). **20**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (ddd, *J* = 16.6, 7.8, 2.5 Hz, 1H), 2.97 (d, *J* = 4.6 Hz, 1H), 2.78 (d, *J* = 4.6 Hz, 1H), 2.07−1.93 (m, 2H), 1.83−1.57 (m, 4H), 1.43−1.26 (m, 3H), 1.16 (s, 3H), 1.11 (s, 3H), 0.94 (s, 3H), 0.86 (s, 9H), −0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.5 (d), 65.3 (s), 62.8 (d), 51.5 (t), 46.8 (s), 45.7 (s), 44.2 (t), 40.7 (t), 35.4 (t), 29.7 (q), 25.7 (q, 3C), 23.6 (q), 21.4 (t), 19.1 (q), 17.9 (s), −4.6 (q), −5.0 (q); IR (neat) 1250, 1070, 830, 780 cm^{-1}; MS *m/e* (rel intensity) 324 (M^+, trace), 175 (100), 75 (76); HRMS calcd for $C_{19}H_{36}O_2Si$ 324.2485, found 324.2531. **21**: white solid, mp 58.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (td, *J* = 8.9, 2.4 Hz, 1H), 2.35 (d, 18.6 Hz, 1H), 2.15 (m, 1H), 2.02 (d, *J* = 18.6 Hz, 1H), 1.99 (m, 1H), 1.85 (m, 1H), 1.71 (tdd, *J* = 14.2, 8.9, 2.4 Hz, 1H), 1.61−1.52 (m, 2H), 1.42 (ddd, *J* = 11.4, 5.4, 2.4 Hz, 1H), 1.28 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.8 (s), 74.5 (d), 68.4 (d), 49.2 (t), 43.7 (s), 43.1 (s), 40.4 (t), 35.5 (t), 30.1 (q), 25.7 (q, 3C), 22.5 (q), 21.0 (t), 18.5 (q), 17.8 (s), −4.7 (q), −5.0 (q); IR (KBr) 1730, 1250, 1070, 830, 770 cm^{-1}; MS *m/e* (rel intensity) 309 (M^+ − H, trace), 253 (100), 75 (57). Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found: C, 69.58; H, 11.07.

To a solution of $HIO_4{\cdot}2H_2O$ (880 mg, 3.86 mmol) in THF (5 mL) was added a solution of **20** (446 mg, 1.37 mmol) in ether (20 mL) dropwise at 0 °C under N_2. The mixture was stirred at 0 °C for 45 min, and ice−water was added. The mixture was extracted with ether, and the combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (three times) and brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/petroleum ether, 0.5:99.5) gave **21** (358 mg, 84%).

(1*R,2*R**,6*S**)-2-(*tert*-Butyldimethylsiloxy)-8-methoxy-6,9,9-trimethylbicyclo[4.2.1]non-7-ene (22) and (1*R**,2*R**,6*S**,7*S**)-2-(*tert*-Butyldimethylsiloxy)-6,7,9,9-tetramethylbicyclo[4.2.1]nonan-8-one (23).** To a solution of LDA prepared from diisopropylamine (7.20 mL, 51.4 mmol) and BuLi (1.57 N in hexane, 29.0 mL, 45.2 mmol) in dry THF (45 mL) was added a solution of **21** (3.09 g, 9.96 mmol) in dry THF (30 mL) dropwise during 30 min at −78 °C under argon. The solution was stirred at −78 °C for 1 h, and a solution of MeI (9.00 mL, 145 mmol) in HMPA (29 mL, 167 mmol) was added dropwise. The white suspension was stirred at −78 °C for 1 h and then warmed up to rt. The mixture was stirred at rt for 2 h, and saturated aqueous NH_4Cl was added. The mixture was extracted with ether, and the combined extracts were washed with water (three times) and brine and dried ($MgSO_4$). The same reaction was undertaken using 11.0 g (35.6 mmol) of **21**. The combined crude products were chromatographed on SiO_2 (elution with ether/petroleum ether, 0.7:99.3) to give **22** (1.43 g, 10%), **23** (9.28 g, 63%), and the recovered **21** (3.56 g, 25%). **22**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.01 (s, 1H), 3.97 (td, *J* = 8.6, 2.0 Hz, 1H), 3.60 (s, 3H), 2.10 (d, *J* = 2.0 Hz, 1H), 1.98 (m, 1H), 1.82−1.72 (m, 2H), 1.49 (m, 1H), 1.33−1.27 (m, 2H), 1.15 (s, 3H), 1.02 (s, 3H), 0.91 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.9 (s), 101.2 (d), 71.0 (d), 63.3 (d), 56.2 (q), 48.9 (s), 45.2 (s), 40.5 (t), 36.2 (t), 31.0 (q), 25.8 (q, 3C), 21.43 (t), 21.36 (q), 18.8 (q), 17.9 (s), −4.7 (q), −4.9 (q); IR (neat) 1650, 1330, 1260, 1080, 860, 845, 780 cm^{-1}; MS *m/e* (rel intensity) 324 (M^+, 5), 281 (100), 267 (86), 139 (52); HRMS calcd for $C_{19}H_{36}O_2Si$ 324.2484, found 324.2472. **23**: white solid, mp 64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (td, *J* = 8.3, 2.4 Hz, 1H), 2.19 (d, *J* = 2.4 Hz, 1H), 2.10 (q, *J* = 7.8 Hz, 1H), 1.98−1.87 (m, 2H), 1.76 (m, 1H), 1.59 (m, 1H), 1.37 (m, 1H), 1.26 (s, 3H), 1.20 (d, *J* = 7.8 Hz, 3H), 1.18 (m, 1H), 0.98 (s, 6H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.3 (s), 74.0 (d), 68.9 (d), 50.6 (d), 44.9 (s), 43.9 (s), 42.3 (t), 35.1 (t), 31.3 (q), 25.7 (q, 3C), 20.2 (t), 19.5 (q), 19.0 (q), 17.9 (s), 15.6 (q), −4.7 (q), −4.9 (q); IR (KBr) 1730, 1250, 1055, 880, 840, 780 cm^{-1}; MS *m/e* (rel intensity) 323 (M^+ − 1, trace), 267 (100). Anal. Calcd for $C_{19}H_{36}O_2Si$: C, 70.31; H, 11.18. Found: C, 70.06; H, 11.42.

To a solution of **22** (1.00 g, 3.09 mmol) in MeOH (20 mL) was added citric acid monohydrate (1.94 g, 9.24 mmol) at 0

°C. The mixture was stirred at 0 °C for 0.5 h and then at rt for 6 h. After addition of the same amount of citric acid monohydrate, the mixture was stirred at rt for another 5 h. Water was added, and the mixture was extracted with ether. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/hexane, 1:99) gave **21** (0.92 g, 97%).

(1*R,2*R**,6*R**)-2-(*tert*-Butyldimethylsiloxy)-8-(2-propenyloxy)-6,7,9,9-tetramethylbicyclo[4.2.1]non-7-ene (24) and (1*R**,2*R**,6*R**,7*S**)-7-Allyl-2-(*tert*-butyldimethylsiloxy)-6,7,9,9-tetramethylbicyclo[4.2.1]nonan-8-one (25).** To a solution of LDA (70.7 mmol) prepared as described above in dry THF (70 mL) and HMPA (23.5 mL) was added a solution of **23** (3.00 g, 9.24 mmol) in dry THF (70 mL) dropwise during 45 min at −78 °C under argon. The mixture was stirred at −78 °C for 45 min, and allyl iodide (13.1 mL, 143 mmol) was added dropwise during 45 min. The mixture was stirred at −78 °C for 45 min and then warmed up to rt and stirred for 2 h. Workup as described above gave **24** (2.36 g, 70%) and **25** (0.68 g, 20%) after column chromatography on SiO_2 (elution with ether/hexane, 0.3:99.7). **24**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 5.99 (m, 1H), 5.33 (dd, J = 17.1, 1.6 Hz, 1H), 5.21 (dd, J = 10.5, 1.1 Hz, 1H), 4.38 (ddt, J = 12.8, 5.5, 1.6 Hz, 1H), 4.18 (ddt, J = 12.8, 5.9, 1.1 Hz, 1H), 3.95 (td, J = 8.6, 1.6 Hz, 1H), 2.26 (s, 1H), 1.98 (m, 1H), 1.80−1.65 (m, 2H), 1.45−1.22 (m, 6H, containing d, J = 1.1 Hz, at 1.41), 1.17 (s, 3H), 0.95 (s, 3H), 0.89 (s, 9H), 0.82 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.2 (s), 134.9 (d), 119.5 (s),117.2 (t), 70.6 (d), 69.8 (t), 59.3 (d), 50.0 (s), 44.2 (s), 38.1 (t), 36.4 (t), 31.1 (q), 25.8 (q, 3C), 21.2 (t), 19.0 (q), 18.8 (q), 17.8 (s), 8.1 (q), −4.6 (q), −4.9 (q); IR (neat) 1690, 1640, 1250, 1060, 830, 770 cm^{-1}; MS m/e (rel intensity) 364 (M^+, 6), 179 (100); HRMS calcd for $C_{22}H_{40}O_2Si$ 364.2798, found 364.2783. **25**: white solid, mp 41 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 5.83 (dddd, J = 14.8, 9.4, 7.7, 6.8 Hz, 1H), 5.03 (d, J = 9.4 Hz, 1H), 4.96 (d, J = 14.8 Hz, 1H), 4.23 (td, J = 8.6, 2.7 Hz, 1H), 2.74 (dd, J = 13.8, 6.8 Hz, 1H), 2.24 (d, J = 2.7 Hz, 1H), 2.00 (dd, J = 13.8, 7.7 Hz, 1H), 1.89−1.73 (m, 3H), 1.58−1.48 (m, 2H), 1.36 (s, 3H), 1.20 (s, 3H), 1.10 (m, 1H), 1.06 (s, 3H), 0.93 (s, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 224.4 (s), 134.8 (d), 116.6 (t), 75.3 (d), 67.4 (d), 53.4 (s), 49.1 (s), 43.1 (t), 43.0 (s), 36.8 (t), 34.1 (t), 32.8 (q), 25.8 (q, 3C), 21.9 (q), 21.8 (t), 20.8 (q), 17.8 (s), 16.8 (q), −4.6 (q), −5.0 (q); IR (KBr) 1720, 1630, 1250, 1070, 830, 770 cm^{-1}; MS m/e (rel intensity) 349 (M^+ − 15, trace), 307 (77), 223 (100), 206 (95), 75 (94). Anal. Calcd for $C_{22}H_{40}O_2Si$: C, 72.47; H, 11.06. Found: C, 72.84; H, 11.19.

A solution of **24** (1.69 g, 4.64 mmol) in *o*-xylene (50 mL) was stirred at 138 °C under N_2 for 36 h. Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/hexane, 0.1:99.9) gave **25** (1.49 g, 88%).

(1*R,2*R**,6*R**,7*S**)-7-Allyl-2-(*tert*-butyldimethylsiloxy)-6,7,9,9-tetramethylbicyclo[4.2.1]nonan-8-ol (26).** To a solution of **25** (989 mg, 2.72 mmol) in dry ether (10 mL) was added DIBALH (1.5 M in toluene, 2.72 mL, 4.08 mmol) at −78 °C under N_2. The mixture was stirred at −78 °C for 3 h, and more DIBALH (0.90 mL, 1.35 mmol) was added. The mixture was stirred for another 1 h, and water was added carefully. The white precipitate was filtered off, and the filtrate was extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/hexane, 0.5:99.5) gave **26** (998 mg, 99%) as a colorless oil: ^1H NMR (600 MHz, $CDCl_3$) δ 5.93 (m, 1H), 5.11 (d, J = 10.0 Hz, 1H), 5.08 (d, J = 17.1 Hz, 1H), 4.46 (dd, J = 9.0, 3.9 Hz, 1H), 4.29 (td, J = 6.2, 3.3 Hz, 1H), 2.40 (dd, J = 13.6, 8.2 Hz, 1H), 2.23 (dd, J = 9.0, 3.3 Hz, 1H), 1.98−1.91 (m, 2H), 1.76−1.67 (m, 2H), 1.63-1.55 (m, 2H), 1.47 (m, 1H), 1.27−1.18 (m, 4H, containing s at 1.22), 1.01 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.74 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.7 (d), 117.8 (t), 76.8 (d), 70.2 (d), 59.1 (d), 50.8 (s), 48.0 (s), 47.5 (t), 46.0 (s), 36.7 (t), 33.8 (t), 31.6 (q), 25.9 (q, 3C), 23.0 (q), 21.5 (t), 19.5 (q), 19.1 (q), 17.9 (s), −4.7 (q), −4.9 (q); IR (neat) 3450, 1630, 1250, 1060, 830, 770 cm^{-1}; MS m/e (rel intensity) 348 (M^+ − 18, trace), 175 (100), 109 (60), 75 (94).

(1*R,2*R**,6*R**,7*S**)-7-Allyl-2-(*tert*-butyldimethylsiloxy)-8-[[(methylthio)thiocarbonyl]oxy]-6,7,9,9-tetramethylbicyclo[4.2.1]nonane (27).** A sample of NaH (60% dispersion in mineral oil, 2.00 g, 50 mmol) was washed three times with petroleum ether, and the solvent was pumped out. To the oil-free NaH was added imidazole (406 mg, 5.96 mmol), HMPA (6.78 mL, 39.0 mmol), and dry THF (45 mL) under N_2. To the mixture was added a solution of **26** (4.79 g, 13.1 mmol) in dry THF (130 mL) at rt. The brown mixture was stirred at rt for 30 min, and CS_2 (6.8 mL, 115.5 mmol) was added. The mixture was stirred at reflux for 5 h, and more CS_2 (4.6 mL, 78.1 mmol) was added. The mixture was stirred at reflux for 10 h, and MeI (3.71 mL, 59.6 mmol) was added. The mixture was stirred at reflux for another 2 h, and then ice−water was added to the cooled mixture. The mixture was extracted with ether, and the combined extracts were washed successively with saturated aqueous Na_2SO_3, saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography on SiO_2 (elution with hexane) gave **27** (5.77 g, 97%) as a pale yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ 6.09 (d, J = 9.2 Hz, 1H), 5.77 (m, 1H), 5.08−5.03 (m, 2H), 3.66 (m, 1H), 2.64 (dd, J = 9.2, 3.3 Hz, 1H), 2.57−2.52 (m, 4H, containing s at 2.57), 1.98 (dd, J = 14.0, 6.9 Hz, 1H), 1.92 (m, 1H), 1.78 (m, 1H), 1.74−1.65 (m, 2H), 1.55 (m, 1H), 1.25 (s, 3H), 1.22 (m, 1H), 1.09 (s, 6H), 0.86 (s, 9H), 0.79 (s, 3H), −0.01 (s, 3H), −0.04 (s, 3H); IR (neat) 1640, 1220, 1060 cm^{-1}; MS m/e (rel intensity) 423 (M^+ − 33, 6), 165 (100).

(1*R,2*R**,6*R**,7*R**)-7-Allyl-2-(*tert*-butyldimethylsiloxy)-6,7,9,9-tetramethylbicyclo[4.2.1]nonane (28).** To a solution of **27** (5.77 g, 12.6 mmol) and AIBN (206 mg, 1.26 mmol) in dry toluene (50 mL) was added a solution of Bu_3SnH (7.80 mL, 29.0 mmol) in dry toluene (10 mL) at rt under argon. The mixture was stirred at 60 °C for 2 h and concentrated in vacuo. The residue was chromatographed on SiO_2 (elution with hexane) to give **28** (3.17 g, 72%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.05 (d, J = 10.5 Hz, 1H), 5.00 (d, J = 17 Hz, 1H), 3.74 (ddd, J = 7.5, 7.5, 2.9 Hz, 1H), 2.52 (dd, J = 14.1, 7.6 Hz, 1H), 2.32 (ddd, J = 14.9, 11.1 Hz, 1H), 1.96−1.91 (m, 2H), 1.86 (dd, J = 14.1, 6.5 Hz, 1H), 1.78−1.66 (m, 2H), 1.61 (m, 1H), 1.55−1.51 (m, 2H), 1.19 (s, 3H), 1.04 (s, 3H), 1.02 (dd, J = 14.9, 2.9 Hz, 1H), 1.01 (s, 3H), 0.88 (s, 9H), 0.72 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.5 (d), 116.5 (t), 77.5 (d), 55.5 (d), 51.5 (s), 47.6 (s), 46.5 (t), 43.9 (s), 39.3 (t), 36.9 (t), 33.9 (t), 32.3 (q), 25.9 (q, 3C), 24.3 (q), 22.7 (t), 22.5 (q), 18.4 (q), 17.9 (s), −4.7 (q), −4.9 (q); IR (neat) 1630, 1250, 1060, 830, 770 cm^{-1}; MS m/e (rel intensity) 335 (M^+ − 15, trace), 293 (100), 75 (74).

(1*R,2*R**,6*R**,7*S**)-2-(*tert*-Butyldimethylsiloxy)-7-(2,3-dihydroxypropyl)-6,7,9,9-tetramethylbicyclo[4.2.1]nonane (29).** To a solution of NMO monohydrate (486 mg, 3.63 mmol) and OsO_4 (69 mg, 0.28 mmol) in *t*-BuOH (14 mL) and water (1.4 mL) was added a solution of **28** (1.05 g, 2.99 mmol) in THF (6 mL) at rt. The mixture was stirred at rt for 4 h, and 0.2 M $NaHSO_3$ was added to the cooled mixture. The mixture was extracted with chloroform, and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/hexane, 75:25) gave a diasteromeric mixture (1.03 g, 89%) of **29A** and **29B** in a 56:44 ratio which was determined by NMR spectra. A small amount of pure sample of each isomer was obtained. **29A**: white solid, mp 142−146 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 3.83 (m, 1H), 3.75 (td, J = 7.7, 2.6 Hz, 1H), 3.54 (dd, J = 10.8, 3.1 Hz, 1H), 3.38 (dd, J = 10.8, 9.4 Hz, 1H), 2.74 (dd, J = 14.8, 11.2 Hz, 1H), 2.13−1.91 (m, 5H), 1.77 (m, 1H), 1.71−1.46 (m, 4H), 1.19 (s, 3H), 1.15 (dd, J = 14.9, 2.9 Hz, 1H), 1.10 (s, 3H), 1.04 (m, 1H), 0.97 (s, 3H), 0.88 (s, 9H), 0.68 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 77.5 (d), 71.3 (d), 68.3 (t), 55.4 (d), 51.6 (s), 47.7 (s), 44.8 (t), 43.8 (s), 39.2 (t), 37.0 (t), 34.1 (t), 32.2 (q), 25.8 (q, 3C), 25.0 (q), 22.9 (t), 22.4 (q), 18.3 (q), 17.9 (s), −4.7 (q), −4.9 (q); IR (KBr) 3350, 1260, 1070, 840, 770 cm^{-1}; MS m/e (rel intensity) 384 (M^+, 1), 327 (100); HRMS calcd for $C_{22}H_{44}O_3Si$ 384.3060, found 384.3057. Anal. Calcd for

$C_{22}H_{44}O_3Si$: C, 68.69; H, 11.53. Found: C, 68.42; H, 11.66. **29B**: white solid, mp 102–105 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 3.84 (m, 1H), 3.75 (td, J = 7.3, 2.8 Hz, 1H), 3.57 (dd, J = 10.8, 3.0 Hz, 1H), 3.40 (dd, J = 10.8, 8.8 Hz, 1H), 2.31 (br s, 2H), 2.15 (dd, J = 14.9, 11.1 Hz, 1H), 1.94 (m, 2H), 1.85 (br d, J = 14.7 Hz, 1H), 1.78–1.48 (m, 5H), 1.23–1.17 (m, 5H, containing s at 1.18), 1.15 (s, 3H), 0.96 (s, 3H), 0.88 (s, 9H), 0.70 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 77.3 (d), 70.8 (d), 68.2 (t), 55.4 (d), 51.8 (s), 47.6 (s), 45.1 (t), 44.1 (s), 40.0 (t), 36.7 (t), 33.7 (t), 32.4 (q), 25.8 (q, 3C), 24.9 (q), 22.6 (t), 22.5 (q), 18.5 (q), 17.9 (s), −4.7 (q), −4.9 (q); IR (KBr) 3400, 1260, 1070, 840, 780 cm^{-1}; MS m/e (rel intensity) 384 (M^+, 1), 327 (100); HRMS calcd for $C_{22}H_{44}O_3Si$ 384.3060, found 384.3083. Anal. Calcd for $C_{22}H_{44}O_3Si$: C, 68.69; H, 11.53. Found: C, 68.53; H, 11.60.

(1*R,2*R**,6*R**,7*S**)-2-(*tert*-Butyldimethylsiloxy)-7-(formylmethyl)-6,7,9,9-tetramethylbicyclo[4.2.1]nonane (30).** To a solution of a mixture of **29** (3.33 g, 8.66 mmol) in THF (50 mL) and water (25 mL) was added $NaIO_4$ (2.42 g, 11.3 mmol) at 0 °C under N_2. The mixture was stirred at rt for 1.5 h and poured into ice–brine. The mixture was extracted with ether, and the combined extracts were dried ($MgSO_4$). Evaporation of the solvent gave the crude products **30**. An analytical sample was obtained by flash chromatography on SiO_2 (elution with ether/hexane, 20:80). **30**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 9.87 (t, J = 2.6 Hz, 1H), 3.76 (td, J = 7.4, 2.4 Hz, 1H), 2.78 (d, J = 15.9 Hz, 1H), 2.45 (dd, J = 15.0, 11.0 Hz, 1H), 2.27 (dd, J = 15.8, 2.3 Hz, 1H), 2.02 (d, J = 10.9 Hz, 1H), 1.96 (m, 1H), 1.79–1.70 (m, 2H), 1.62 (m, 1H), 1.56–1.53 (m, 2H), 1.40 (dd, J = 15.1, 2.5 Hz, 1H), 1.212 (s, 3H), 1.210 (s, 3H), 1.06 (s, 3H), 0.88 (s, 9H), 0.72 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.0 (d), 77.1 (d), 56.6 (t), 55.6 (d), 51.9 (s), 47.7 (s), 43.5 (s), 41.1 (t), 36.3 (t), 33.7 (t), 32.2 (q), 25.8 (q, 3C), 25.3 (q), 22.49 (q), 22.48 (t), 18.9 (q), 17.9 (s), −4.7 (q), −4.9 (q); IR (neat) 1710, 1250, 1100, 1060, 830, 770 cm^{-1}; MS m/e (rel intensity) 352 (M^+, trace), 295 (100), 75 (68); HRMS calcd for $C_{21}H_{40}O_2Si$ 352.2798, found 352.2789.

(1*R,2*R**,6*R**,7*S**)-2-(*tert*-Butyldimethylsiloxy)-7-[2-cycano-2-(1-ethoxyethoxy)ethyl]-6,7,9,9-tetramethylbicyclo[4.2.1]nonane (8).** To a solution of the above aldehyde **30** in dry CH_2Cl_2 (70 mL) was added TMSCN (1.39 mmol, 10.4 mmol) and ZnI_2 (557 mg, 1.73 mmol) at 0 °C under argon. The mixture was stirred at rt for 1 h and poured into ice–water. The mixture was extracted with ether, and the combined extracts were dried ($MgSO_4$). Evaporation of the solvent gave the crude product **31**: IR (neat) 1260, 1100, 1060, 840, 770 cm^{-1}. To a solution of the cyanohyrin TMS ether **31** in THF (50 mL) and water (50 mL) was added NH_4F (482 mg, 13.0 mmol) at 0 °C under N_2. The mixture was stirred at rt for 1.5 h and poured into ice–water. The mixture was extracted with ether, and the combined extracts were dried ($MgSO_4$). Evaporation of the solvent gave the crude product **32**: IR (neat) 3400, 1250, 1060, 830, 780 cm^{-1}. To a solution of the cyanohyrin **32** in dry CH_2Cl_2 (50 mL) was added ethyl vinyl ether (2.49 mL, 26.0 mmol) and PPTS (1.09 g, 4.33 mmol) at 0 °C under N_2. The mixture was stirred at rt for 18 h, and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/hexane, 2:98 to 10:90) gave a diasteromeric mixture (3.48 g, 88%) of **8A**, **8B**, **8C**, and **8D** in an about 3:2:2:1 ratio, which was determined by NMR spectra and GLC analysis. A small amount of pure samples of each isomer was obtained. **8A**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 4.94 (q, J = 5.3 Hz, 1H), 4.55 (dd, J = 5.7, 5.6 Hz, 1H), 3.73 (td, J = 7.5, 2.8 Hz, 1H), 3.69 (dq, J = 9.3, 7.1 Hz, 1H), 3.55 (dq, J = 9.3, 7.1 Hz, 1H), 2.44–2.33 (m, 2H), 1.96–1.91 (m, 2H), 1.79–1.68 (m, 3H, containing dd, J = 14.7, 15.3 Hz at 1.78), 1.62–1.50 (m, 3H), 1.38 (d, J = 5.4 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.19 (s, 3H), 1.16 (m, 1H), 1.10 (s, 3H), 1.04 (s, 3H), 0.99 (s, 9H), 0.72 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 119.9 (s), 98.8 (d), 77.2 (d), 62.1 (d), 60.9 (t), 55.4 (d), 52.0 (s), 47.6 (s), 45.9 (t), 43.9 (s), 39.1 (t), 36.7 (t), 33.8 (t), 32.1 (q), 25.8 (q, 3C), 24.6 (q), 22.6 (t), 22.4 (q), 19.6 (q), 18.4 (q), 17.9 (s), 15.2 (q), −4.7 (q), −4.9 (q); IR (neat) 1250, 1060, 830, 770 cm^{-1}; MS m/e (rel intensity) 450 (M^+ − 1, 1), 394 (100), 73 (86); HRMS calcd for $C_{26}H_{49}NO_3Si$ 451.3482, found 451.3516. **8B**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 4.95 (q, J = 5.3 Hz, 1H), 4.55 (dd, J = 7.1, 5.1 Hz, 1H), 3.74 (td, J = 7.6, 2.8 Hz, 1H), 3.64 (dq, J = 9.2, 7.1 Hz, 1H), 3.54 (dq, J = 9.2, 7.1 Hz, 1H), 2.53 (dd, J = 14.7, 7.1 Hz, 1H), 2.40 (dd, J = 15.1, 11.0 Hz, 1H), 2.01 (m, 1H), 1.95 (m, 1H), 1.77 (m, 1H), 1.69 (m, 1H), 1.62 (dd, J = 14.6, 5.1 Hz, 1H), 1.61–1.52 (m, 3H), 1.37 (d, J = 5.3 Hz, 3H), 1.26–1.20 (m, 7H, containing t, J = 7.1 Hz at 1.24, and s at 1.20), 1.09 (s, 3H), 1.07 (s, 3H), 0.88 (s, 9H), 0.73 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 119.8 (s), 98.5 (d), 77.0 (d), 61.8 (d), 60.7 (t), 55.3 (d), 52.2 (s), 47.6 (s), 45.3 (t), 43.6 (s), 39.5 (t), 36.7 (t), 33.9 (t), 32.1 (q), 25.8 (q, 3C), 24.1 (q), 22.7 (t), 22.4 (q), 19.6 (q), 18.3 (q), 17.9 (s), 15.2 (q), −4.7 (q), −4.9 (q); IR (neat) 1250, 1060, 830, 770 cm^{-1}; MS m/e (rel intensity) 450 (M^+ − 1, trace), 394 (100), 73 (76); HRMS calcd for $C_{26}H_{48}NO_3Si$ (M^+ − H) 450.3404, found 450.3399. **8C**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 4.86 (q, J = 5.3 Hz, 1H), 4.29 (t, J = 5.7 Hz, 1H), 3.74–3.69 (m, 2H), 3.61 (m, 1H), 2.42 (dd, J = 14.8, 5.3 Hz, 1H), 2.34 (dd, J = 14.8, 11.1 Hz, 1H), 1.96–1.91 (m, 2H), 1.79–1.68 (m, 3H, containing dd, J = 14.8, 5.3 Hz at 1.75), 1.60–1.49 (m, 3H), 1.41 (d, J = 5.3 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 1.20 (s, 3H), 1.16 (m, 1H), 1.09 (s, 3H), 1.04 (s, 3H), 0.88 (s, 9H), 0.72 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 120.7 (s), 100.7 (d), 77.1 (d), 62.8 (d), 61.1 (t), 55.4 (d), 52.0 (s), 47.6 (s), 46.5 (t), 43.9 (s), 39.0 (t), 36.7 (t), 33.8 (t), 32.0 (q), 25.8 (q, 3C), 24.7 (q), 22.7 (t), 22.4 (q), 19.6 (q), 18.4 (q), 17.9 (s), 14.8 (q), −4.7 (q), −4.9 (q); IR (neat) 1250, 1050, 830, 770 cm^{-1}; MS m/e (rel intensity) 450 (M^+ − 1, 1), 394 (100), 73 (86); HRMS calcd for $C_{26}H_{49}NO_3Si$ 451.3482, found 451.3513. **8D**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 4.85 (q, J = 5.4 Hz, 1H), 4.31 (dd, J = 6.2, 6.0 Hz, 1H), 3.75–3.69 (m, 2H), 3.59 (dq, J = 9.2, 7.1 Hz, 1H), 2.52 (dd, J = 14.7, 6.8 Hz, 1H), 2.37 (dd, J = 15.1, 11.0 Hz, 1H), 2.02 (m, 1H), 1.95 (m, 1H), 1.79–1.68 (m, 2H), 1.65–1.49 (m, 4H, containing dd, J = 14.8, 5.3 Hz at 1.64), 1.40 (d, J = 5.4 Hz, 3H), 1.26–1.20 (m, 7H, containing t, J = 7.1 Hz at 1.25, and s at 1.20), 1.08 (s, 3H), 1.06 (s, 3H), 0.88 (s, 9H), 0.72 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 120.7 (s), 100.4 (d), 77.1 (d), 62.1 (d), 61.3 (t), 55.4 (d), 52.2 (s), 47.6 (s), 46.0 (t), 43.6 (s), 39.6 (t), 36.7 (t), 33.9 (t), 32.1 (q), 25.8 (q, 3C), 24.2 (q), 22.7 (t), 22.4 (q), 19.6 (q), 18.3 (q), 17.9 (s), 14.9 (q), −4.7 (q), −4.9 (q); IR (neat) 1250, 1060, 830, 770 cm^{-1}; MS m/e (rel intensity) 450 (M^+ − 1, trace), 394 (100), 73 (72); HRMS calcd for $C_{26}H_{48}NO_3Si$ (M^+ − H) 450.3404, found 450.3427.

Synthesis of Segment 7. 2-Allyl-1,4-dimethoxy-6-methylbenzene (34). To a solution of **33**[18] (39.4 g, 171 mmol) in dry ether (770 mL) was added BuLi (1.57 N in hexane, 154 mL, 257 mmol) dropwise during 1 h at rt under argon. The mixture was stirred at rt for 30 min, and CuI (17.3 g, 91.0 mmol) was added. After the mixture was stirred at rt for 2 h, allyl bromide (25.0 g, 207 mmol) was added. The mixture was stirred at rt for 16 h and then poured into saturated aqueous NH_4Cl. The mixture was extracted with ether, and the combined extracts were washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography on SiO_2 (elution with ether/hexane, 2:98) gave **34** (24.4 g, 75%) as a colorless oil: ^1H NMR (600 MHz, $CDCl_3$) δ 6.57–6.60 (m, 2H), 5.98 (m, 1H), 5.12–5.08 (m, 2H), 3.76 (s, 3H), 3.69 (s, 3H), 3.41 (br d, J = 6.6 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5 (s), 150.4 (s), 137.2 (d), 133.7 (s), 131.9 (s), 115.8 (t), 114.2 (d), 112.8 (d), 60.6 (q), 55.4 (q), 34.2 (t), 16.4 (q); IR (neat) 1630, 1600, 1220, 1060, 1020, 860 cm^{-1}; MS m/e (rel intensity) 192 (M^+, 100), 177 (50); HRMS calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1161.

2-(2,3-Dihydroxypropyl)-1,4-dimethoxy-6-methylbenzene (35). Reaction of **34** (1.26 g, 6.56 mmol) with OsO_4 and NMO monohydrate as described for the preparation of **29** gave **35** (1.07 g, 95%) after column chromatography on SiO_2 (elution with ether). **35**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 6.61 (d, J = 3.0 Hz, 1H), 6.58 (d, J = 3.0 Hz, 1H), 3.90 (m, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.59 (dd, J = 11.4, 3.6 Hz, 1H), 3.47 (dd, J = 11.4, 5.6 Hz, 1H), 2.86–2.76 (m, 2H),

2.70 (br s, 2H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7 (s), 150.6 (s), 132.0 (s), 131.4 (s), 115.0 (d), 113.8 (d), 72.8 (d), 65.8 (t), 60.6 (q), 55.4 (q), 34.6 (t), 16.4 (q); IR (neat) 3400, 1600, 1220, 1080, 1060, 1020, 860 cm^{-1}; MS *m/e* (rel intensity) 226 (M^+, 82), 151 (100), 135 (47); HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1207.

Ethyl (*Z*)- and (*E*)-(2,5-Dimethoxy-3-methylphenyl)-2-methyl-2-butenoates (37 and 38). Reaction of **35** (1.00 g, 4.43 mmol) with $NaIO_4$ as described for the preparation of **30** gave the crude product **36**: IR (neat) 1720, 1600, 1230, 1060, 1010, 860 cm^{-1}. A mixture of the aldehyde **36** and ethyl 2-(triphenylphosphoranylidene)propionate[19] (1.92 g, 6.64 mmol) in dry CH_2Cl_2 (15 mL) was stirred at rt for 1.5 h under N_2. After addition of the ylide (0.81 g, 2.21 mmol) again, the mixture was stirred for 1 h. The solvent was evaporated *in vacuo*, and hexane was added to the residue. The white precipitate ($P(O)Ph_3$) was filtered off, and the filtrate was concentrated. Flash chromatography of the crude product on SiO_2 (elution with ether/hexane, 6:94) gave **37** (0.045 g, 4%) and **38** (1.08 g, 88%). **37**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.59 (s, 2H), 6.04 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.84 (br d, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.68 (s, 3H), 2.29 (s, 3H), 1.96 (t, J = 1.0 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H); IR (neat) 1710, 1640, 1600, 1220, 1060, 1010, 860 cm^{-1}; MS *m/e* (rel intensity) 278 (M^+, 100), 203 (48); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1507. **38**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (m, 1H), 6.61 (d, J = 3 Hz, 1H), 6.53 (d, J = 3.0 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.69 (s, 3H), 3.52 (br d, J = 7.4 Hz, 2H), 2.29 (s, 3H), 1.98 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); IR (neat) 1710, 1640, 1600, 1220, 1060, 1010, 860 cm^{-1}; MS *m/e* (rel intensity) 278 (M^+, 100), 189 (70); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1497.

(*E*)-(2,5-Dimethoxy-3-methylphenyl)-2-methyl-2-buten-1-ol (39). Reaction of **38** (979 mg, 3.52 mmol) with DIBALH as described for the preparation of **26** gave **39** (819 mg, 97%) as a colorless oil after flash chromatography on SiO_2 (elution with ether/hexane, 30:70); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (d, J = 3.0 Hz, 1H), 6.55 (d, J = 3.0 Hz, 1H), 5.58 (m, 1H), 4.04 (s, 2H), 3.75 (s, 3H), 3.69 (s, 3H), 3.40 (br d, J = 7.1 Hz, 2H), 2.29 (s, 3H), 1.80 (s, 3H), 1.64 (s, 1H); IR (neat) 3400, 1600, 1220, 1060, 1010, 850 cm^{-1}; MS *m/e* (rel intensity) 236 (M^+, 100), 187 (53); HRMS calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1434.

2-[(*E*)-4-Chloro-3-methyl-2-butenyl]-1,4-dimethoxy-6-methylbenzene (7). A mixture of **39** (1.00 g, 4.23 mmol) and PPh_3 (1.11 g, 4.23 mmol) in dry CCl_4 was stirred at 85 °C for 30 h. The solvent was evaporated *in vacuo*, and hexane was added to the residue. The white precipitate ($P(O)Ph_3$) was filtered off, and the filtrate was concentrated. Flash chromatography of the crude product on SiO_2 (elution with ether/hexane, 2:98) gave **7** (0.96 g, 89%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.59 (d, J = 3.0 Hz, 1H), 6.54 (d, J = 3.0 Hz, 1H), 5.70 (t, J = 7.0 Hz, 1H), 4.07 (s, 2H), 3.76 (s, 3H), 3.69 (s, 3H), 3.40 (d, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.88 (s, 3H); IR (neat) 1600, 1290, 1220, 1060, 1010, 860 cm^{-1}; MS *m/e* (rel intensity) 256 (M^+ + 2, 35), 254 (M^+, 100); HRMS calcd for $C_{14}H_{19}ClO_2$ 254.1074, found 254.1053.

Model Study for Introduction of 1,3-Diketone Functionality. (1*R,6*R**)-6,9,9-Trimethylbicyclo[4.2.1]non-3-en-2-one (40).** To a solution of **5** (580 mg, 3.22 mmol) and Et_3N (0.67 mmol, 4.83 mmol) in CCl_4 (7 mL) was added TMSOTf (0.75 mL, 3.87 mmol) dropwise at 0 °C under N_2. The mixture was stirred at rt for 40 min and poured into saturated aqueous $NaHCO_3$. The mixture was extracted with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/hexane, 5:95) gave the silyl enol ether (777 mg, 96%) as a colorless oil: IR (neat) 1650, 1250, 1180, 1155, 1130, 925, 870, 840 cm^{-1}. To a mixture of $Pd(OAc)_2$ (921 mg, 4.03 mmol) and Na_2CO_3 (774 mg, 7.03 mmol) in dry CH_3CN (13 mL) was added a solution of the above enol ether in dry CH_3CN (13 mL) at rt under N_2. The mixture was stirred at rt for 1 h and filtered through SiO_2. The filtrate was concentrated *in vacuo*, and flash chromatography of the residue on SiO_2 (elution with ether/hexane, 6:94) gave **40** (550 mg, 96%) as a white solid: mp 158–161 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (ddd, J = 12.7, 6.4, 2.9 Hz, 1H), 5.86 (m, 1H), 2.68 (m, 1H), 2.39 (m, 1H), 2,29 (m, 1H), 2.06 (m, 1H), 1.96–1.76 (m, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3 (s), 143.1 (d), 129.0 (d), 65.8 (d), 46.6 (s), 45.3 (t), 44.6 (s), 38.8 (t), 27.4 (q), 26.8 (t), 24.7 (q), 19.4 (q); IR (KBr) 1660 cm^{-1}; MS *m/e* (rel intensity) 178 (M^+, 17), 95 (100), 68 (33); HRMS calcd for $C_{12}H_{18}O$ 178.1358, found 178.1372.

(1*R,3*S**,4*S**,6*R**)-3,4-Epoxy-6,9,9-trimethylbicyclo[4.2.1]-nonan-2-one (41).** To a solution of enone **40** (193 mg, 7.80 mmol) in MeOH (8 mL) were added 30% aqueous H_2O_2 (0.68 mL, 6.65 mmol) and then 6 N NaOH (0.34 mL, 2.04 mmol) dropwise at 0 °C. The mixture was stirred at rt for 6 h, and then brine was added. The mixture was extracted with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/hexane, 3:97) gave **41** (199 mg, 94%) as a white solid: mp 186–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (dd, J = 4.4, 1.8 Hz, 1H), 3.28 (ddd, J = 4.4, 2.9, 1.8 Hz, 1H), 2.60 (m, 1H), 2.28–2.15 (m, 2H), 2.07–1.97 (m, 2H), 1.91–1.72 (m, 2H), 0.96 (s, 3H), 0.94 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.5 (s), 64.5 (d), 59.5 (d), 55.5 (d), 44.5 (s), 44.4 (s), 38.6 (t), 37.4 (t), 27.8 (q), 25.6 (q), 23.4 (t), 18.6 (q); IR (KBr) 1680 cm^{-1}; MS *m/e* (rel intensity) 194 (M^+, 32), 109 (97), 95 (100); HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1318.

(1*R,4*S**,6*R**)-6,9,9-Trimethylbicyclo[4.2.1]nonane-2,4-diol (42).** Reaction of **41** (1.60 g, 8.19 mmol) with $LiAlH_4$ (311 mg, 8.19 mmol) as described for the preparation of **17** and **18** at rt gave **42** (1.49 g, 91%) as a white solid after column chromatography on SiO_2 (elution with ether): mp 177–180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.47 (m, 1H), 3.94 (m, 1H), 2.08–1.90 (m, 5H), 1.82–1.77 (m, 2H), 1.67 (br s, 1H), 1.57 (br s, 1H), 1.36 (dd, J = 14.3, 8.5 Hz, 1H), 1.18 (m, 1H), 1.13 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 74.2 (d), 66.2 (d), 56.0 (d), 51.4 (t), 45.9 (s), 44.5 (s), 39.4 (t), 39.2 (t), 30.2 (q), 26.3 (q), 25.9 (t), 20.6 (q); IR (KBr) 3300, 1060, 1040, 1010 cm^{-1}; MS *m/e* (rel intensity) 197 (M^+ – 1, 15), 180 (70), 109 (60), 95 (100), 81 (75), 69 (60), 55 (60), 41 (55). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.37; H, 11.25.

(1*R,6*R**)-6,9,9-Trimethylbicyclo[4.2.1]nonane-2,4-dione (43).** To a mixture of PCC (2.59g, 12.0 mmol), MS4A (powder, 5.0 g), and NaOAc (246 mg, 3.00 mol) in dry CH_2Cl_2 was added a solution of **42** (792 mg, 4.00 mmol) in dry CH_2Cl_2 at rt. The mixture was stirred for 2 h, and ether (100 mL) was added. After stirring at rt for 30 min, the mixture was filtered through SiO_2. The filtrate was concentrated *in vacuo*, and flash chromatography of the residue on SiO_2 (elution with ether/hexane, 30:70) gave **43** (588 mg, 76%) as a white solid: mp 207–209 °C dec; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.40 (s, 2H), 2.81 (d, J = 13.3 Hz, 1H), 2.64 (d, J = 9.4 Hz, 1H), 2.26 (d, J = 13.3 Hz, 1H), 2.02–1.84 (m, 3H), 1.59 (m, 1H), 1.09 (m, 3H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 205.9 (s), 205.5 (s), 65.6 (d), 56.7 (t), 55.7 (t), 48.8 (s), 46.8 (s), 36.0 (t), 27.8 (q), 23.2 (q), 22.7 (t), 19.8 (q); IR (KBr) 3500–2500, 1560, 1210, 870 cm^{-1}, (CCl_4) 1700, 1690 cm^{-1}; MS *m/e* (rel intensity) 194 (M^+, 45), 109 (100), 95 (100), 69 (63); HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1319.

(1*R,6*R**)-4-Methoxy-6,9,9-trimethylbicyclo[4.2.1]-non-3-en-2-one (44), (1*R**,6*R**)-2-Methoxy-6,9,9-trimethylbicyclo[4.2.1]non-2-en-4-one (45), (1*R**,6*R**)-3,3,6,9,9-Pentamethylbicyclo[4.2.1]nonane-2,4-dione (46), (1*R**,6*R**)-4-Methoxy-3,6,9,9-tetramethylbicyclo[4.2.1]non-3-en-2-one (47), and (1*R**,6*R**)-2-Methoxy-3,6,9,9-tetramethylbicyclo[4.2.1]non-2-en-4-one (48).** A mixture of **43** (110 mg, 0.57 mmol), MeI (1.24 mL, 19.8 mmol), and K_2CO_3 (627 mg, 4.54 mmol) in dry acetone (10 mL) was stirred under argon at 60 °C for 3 h. The solvent was evaporated *in vacuo*, and water was added to the residue. The mixture was extracted with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography of the residue on SiO_2 (elution with ether/hexane, 15:85 to 30:70) gave **46** (20 mg, 16%), a mixture of **47** and **48** (25 mg, 20%, 75:25), **44** (43 mg, 36%), and **45** (28 mg, 24%). **44**: white solid; mp 70–71 °C;

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.30 (s, 1H), 3.59 (s, 3H), 2.67 (d, J = 9.0 Hz, 1H), 2.55 (d, J = 18.4 Hz, 1H), 2.20 (d, J = 18.4 Hz, 1H), 2.07 (m, 1H), 1.95–1.77 (m, 3H), 1.03 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.4 (s), 171.0 (s), 102.7 (d), 66.1 (d), 55.3 (q), 47.6 (t), 45.3 (s), 44.8 (s), 37.8 (t), 27.3 (q + t), 24.6 (q), 19.5 (q); IR (KBr) 1630, 1615, 1380, 1210, 1150, 830 cm^{-1}; MS m/e (rel intensity) 208 (M^+, 66), 152 (66), 125 (54), 109 (77), 95 (100), 41 (50); HRMS calcd for $C_{13}H_{20}O_2$ 208.1464, found 208.1444. **45**: white solid; mp 58–59 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.33 (d, J = 2.0 Hz, 1H), 3.61 (s, 3H), 2.64 (d, J = 17.5 Hz, 1H), 2.49 (d, J = 8.9 Hz, 1H), 2.40 (d, J = 17.5 Hz, 1H), 2.23 (m, 1H), 1.91–1.73 (m, 3H), 1.10 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.8 (s), 180.2 (s), 103.1 (d), 58.6 (d), 55.8 (q), 55.6 (t), 45.11 (s), 45.07 (s), 37.0 (t), 31.1 (t), 27.3 (q), 24.6 (q), 19.7 (q); IR (KBr) 1610, 1380, 1210, 1150, 830 cm^{-1}; MS m/e (rel intensity) 208 (M^+, 19), 153 (100); HRMS calcd for $C_{13}H_{20}O_2$ 208.1464, found 208.1444. **46**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.03 (d, J = 12.5 Hz, 1H), 2.69 (dd, J = 9.3, 1.6 Hz, 1H), 2.13 (d, J = 12.5 Hz, 1H), 2.00–1.78 (m, 3H), 1.61 (m, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.0 (s), 212.5 (s), 65.5 (d), 58.0 (s), 50.8 (t), 49.6 (s), 48.3 (s), 34.5 (t), 27.4 (q), 24.9 (q), 24.5 (q), 22.6 (q), 21.5 (t), 20.7 (q); IR (neat) 1710, 1680, 1380 cm^{-1}; MS m/e (rel intensity) 222 (M^+, 29), 109 (100); HRMS calcd for $C_{14}H_{22}O_2$ 222.1619, found 222.1635. A mixture of **47** and **48** (not separated): colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) for **47** δ 3.67 (s, 2.25H), 2.76 (d, J = 8.7 Hz, 0.75H), 2.46 (m, 0.75H), 2.33 (d, J = 18.0 Hz, 0.75H), 1.78 (s, 2.25H), 2.04–1.73 (m, 3H), 1.03 (s, 2.25H), 0.99 (s, 2.25H), 0.98 (s, 2.25H); for **48** 3.66 (s, 0.75H), 2.70 (d, J = 9.3 Hz, 0.25H), 2.63 (m, 0.25H), 2.38 (d, J = 16.1 Hz, 0.25H), 2.04–1.72 (m, 1H), 1.75 (s, 0.75H), 1.12 (s, 0.75H), 1.05 (s, 0.75H), 0.94 (s, 0.75H); IR (neat) 1680, 1620, 1380, 1210, 1130, 1090 cm^{-1}; GC–MS m/e (rel intensity) for **47** 222 (M^+, 56), 109 (100), 113 (50), 110 (50), 95 (60), 43 (51), 41 (57); for **48** 222 (M^+, 42), 147 (100); HRMS calcd for $C_{14}H_{22}O_2$ 222.1619, found for **47** 222.1616, for **48** 222.1593. The regiochemistry of **47** and **48** was assigned according to the ref 21 where the signal of the C9 methine proton (δ 2.76) of **47** appeared at lower field than that (δ 2.70) of **48**.

(1*R,6*R**)-2,4-Dimethoxy-6,9,9-trimethylbicyclo[4.2.1]-nona-2,4-diene (49).** A mixture of **43** (50 mg, 0.26 mmol), Me_3OBF_4 (192 mg, 1.30 mmol), and Proton Sponge (306 mg, 1.43 mmol) in dry CH_2Cl_2 (1.0 mL) was stirred under argon at rt for 8 h. To the mixture were added Me_3OBF_4 (77 mg, 0.52 mmol) and Proton Sponge (122 mg, 0.57 mmol). After the mixture was stirred for another 15 h, Me_3OBF_4 (39 mg, 0.29 mmol) and Proton Sponge (61 mg, 0.29 mmol) were added. The mixture was stirred for another 5 h, and then saturated aqueous $NaHCO_3$ was added. The mixture was extracted with ether, and the combined extracts were washed with 5% aqueous oxalic acid and brine and dried ($MgSO_4$). Evaporation of the solvent followed by rapid column chromatography on SiO_2 (elution with ether/hexane, 20:80 to 50:50) to give **49** (23 mg, 40%), **44** (25 mg, 42%), and **45** (11 mg, 18%). **49**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.68 (s, 1H), 4.35 (s, 1H), 3.51 (s, 3H), 3.48 (s, 3H), 2.24 (d, J = 9.6 Hz, 1H), 2.09 (m, 1H), 2.01 (m, 1H), 1.92–1.86 (m, 2H), 1.04 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3 (s), 150.8 (s), 106.3 (d), 93.9 (d), 55.5 (q), 54.8 (q), 54.2 (d), 46.6 (s), 46.2 (t), 39.5 (s), 32.5 (t), 26.5 (q), 23.1 (q), 19.8 (q); IR (neat) 1655, 1620, 1365, 1220, 1200, 1150, 1030, 810 cm^{-1}; MS m/e (rel intensity) 222 (M^+, 30), 140 (100); HRMS calcd for $C_{14}H_{22}O_2$ 222.1619, found 222.1630.

Completion of the Synthesis. Coupling of 7 and 8. To a solution of LDA (10.0 mmol) prepared as described above in dry THF (25 mL) was added a solution of **8** (3.59 g, 7.69 mmol) and HMPA (0.67 mL, 3.90 mmol) in dry THF (30 mL) dropwise during 15 min at −45 °C under argon. The mixture was stirred at −45 °C for 40 min, and a solution of **7** (2.57 g, 10.0 mmol) in dry THF (20 mL) was added dropwise during 10 min. After stirring at −45 °C for 1.5 h, the mixture was warmed up to 0 °C and stirred for 1 h. Workup as described for the preparation of **23** followed by column chromatography on SiO_2 (elution with ether/hexane, 2:98 to 4:96) gave a diasteromeric mixture (4.26 g, 80%) of the cyanohydrin ethoxyethyl ethers **50A**, **50B**, **50C**, and **50D**. A small amount of analytical samples for **50A** and **50D** (>90% purity) was separated. The ^{13}C NMR signals of **50B** and **50C** could be discerned from the spectra of a mixture of **50A** and **50B**, and **50C** and **50D**, respectively. **50A**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (d, J = 3.0 Hz, 1H), 6.55 (d, J = 3.0 Hz, 1H), 5.47 (t, J = 7.0 Hz, 1H), 5.25 (q, J = 5.2 Hz, 1H), 3.76–3.66 (m, 7H, containing s at 3.75 and s at 3.67), 3.60 (dq, J = 9.0, 7.1 Hz, 1H), 3.52 (dq, J = 9.0, 7.1 Hz, 1H), 3.41–3.33 (m, 2H), 2.87 (d, J = 13.5 Hz, 1H), 2.71 (dd, J = 11.3, 5.1 Hz, 1H), 2.55 (d, J = 13.5 Hz, 1H), 2.30–2.25 (m, 4H, containing s at 2.28), 2.00–1.90 (m, 5H, containing s, at 1.90), 1.80 (m, 1H), 1.65–1.43 (m, 5H), 1.37 (d, J = 5.2 Hz, 3H), 1.25–1.16 (m, 10H, containing t, J = 7.0 Hz, at 1.21, s at 1.18, and s at 1.17), 1.04 (s, 3H), 0.88 (s, 9H), 0.56 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7 (s), 150.4 (s), 134.5 (s), 131.8 (s), 130.7 (d), 130.1 (s), 120.5 (s), 113.8 (d), 113.0 (d), 98.2 (d), 77.3 (d), 76.3 (s), 60.5 (q), 59.9 (t), 55.8 (d), 55.4 (q), 52.9 (s), 51.7 (t), 47.8 (t), 47.2 (s), 43.4 (s), 39.1 (t), 36.7 (t), 34.3 (t), 31.1 (q), 28.8 (t), 25.9 (q, 3C), 25.5 (q), 23.4 (t), 22.5 (q), 20.4 (q), 18.0 (s), 17.8 (q), 17.5 (q), 16.4 (q), 15.3 (q), −4.8 (q), −4.9 (q); IR (neat) 1600, 1250, 1220, 1060, 830, 770 cm^{-1}; MS m/e (rel intensity) 669 (M^+, 16), 177 (50), 73 (100); HRMS calcd for $C_{40}H_{67}NO_5Si$ 669.4789, found 669.4786. **50B**: ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7 (s), 150.4 (s), 134.4 (s), 131.8 (s), 130.8 (d), 129.9 (s), 120.6 (s), 114.0 (d), 112.9 (d), 98.3 (d), 77.0 (d), 75.6 (s), 60.5 (q), 60.1 (t), 55.4 (d + q), 53.3 (s), 52.2 (t), 48.3 (t), 47.3 (s), 44.1 (s), 39.8 (t), 36.6 (t), 33.9 (t), 31.6 (q), 28.9 (t), 25.9 (q, 3C), 25.4 (q), 23.0 (t), 22.7 (q), 20.7 (q), 18.3 (q), 17.9 (s + q), 16.4 (q), 15.3 (q), −4.7 (q), −4.8 (q). **50C**: ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7 (s), 150.4 (s), 134.3 (s), 131.8 (s), 130.9 (d), 129.6 (s), 121.4 (s), 113.9 (d), 112.9 (d), 97.2 (d), 77.3 (d), 74.4 (s), 60.9 (t), 60.5 (q), 55.8 (d), 55.4 (q), 53.1 (s), 50.8 (t), 48.9 (t), 47.2 (s), 43.5 (s), 39.5 (t), 36.8 (t), 34.2 (t), 31.4 (q), 28.8 (t), 25.9 (q, 3C), 25.2 (q), 23.2 (t), 22.6 (q), 21.3 (q), 17.9 (s + q), 17.8 (q), 16.3 (q), 15.1 (q), −4.7 (q), −4.9 (q). **50D**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (d, J = 3.0 Hz, 1H), 6.54 (d, J = 3.0 Hz, 1H), 5.51 (t, J = 7.1 Hz, 1H), 5.11 (q, J = 5.21 Hz, 1H), 3.78–3.65 (m, 8H, containing s at 3.75 and s at 3.68), 3.60 (dq, J = 8.6, 7.2 Hz, 1H), 3.39 (dd, J = 15.6, 7.6 Hz, 1H), 3.35 (dd, J = 15.6, 7.1 Hz, 1H), 2.84 (dd, J = 15.5, 11.1 Hz, 1H), 2.64 (d, J = 13.4 Hz, 1H), 2.47 (d, J = 13.4 Hz, 1H), 2.32 (d, J = 15.3 Hz, 1H), 2.28 (s, 3H), 2.02 (m, 1H), 1.95 (m, 1H), 1.89 (s, 3H), 1.76 (m, 1H), 1.61 (m, 1H), 1.50 (m, 1H), 1.33–1.18 (m, 15H, containing d, J = 5.1 Hz, at 1.33, t, J = 7.1 Hz, at 1.25, s at 1.23, and s at 1.18), 1.11 (m, 1H), 1.00 (s, 3H), 0.88 (s, 9H), 0.60 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7 (s), 150.4 (s), 134.3 (s), 131.9 (s), 130.9 (d), 129.5 (s), 121.4 (s), 114.0 (d), 112.9 (d), 97.3 (d), 77.2 (d), 74.2 (s), 61.1 (t), 60.5 (q), 55.5 (d), 55.4 (q), 53.3 (s), 51.1 (t), 48.6 (t), 47.2 (s), 44.0 (s), 39.6 (t), 36.6 (t), 34.0 (t), 31.7 (q), 28.9 (t), 25.8 (q, 3C), 24.6 (q), 23.1 (t), 22.7 (q), 21.3 (q), 18.1 (q), 17.9 (s + q), 16.4 (q), 15.0 (q), −4.7 (q), −4.9 (q); IR (neat) 1600, 1245, 1220, 1060, 830, 770 cm^{-1}; MS m/e (rel intensity) 669 (M^+, 11), 177 (62), 73 (100); HRMS calcd for $C_{40}H_{67}NO_5Si$ 669.4789, found 669.4744.

Selective Deprotection of Cyanohyrin Ethoxyethyl Ether in 50. A mixture of concd HCl (3.0 mL) and $MgSO_4$ (30 g) was stirred at rt for 1 h. The mixture was filtered, and the filtrate was added to **50** (8.55 g, 12.8 mmol) at rt under N_2. The mixture was stirred at rt for 1 h and concentrated *in vacuo*. To the residue was added 2% aqueous NaOH (60 mL) and ether (120 mL). After stirring at rt for 4 h, the mixture was extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography on SiO_2 (elution with ether/hexane, 2:98 to 5:95) gave the ketone **51** (7.11 g, 98%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 2H), 5.41 (t, J = 7.1 Hz, 1H), 3.78–3.72 (m, 4H, containing s at 3.76), 3.69 (s, 3H), 3.39 (d, J = 7.1 Hz, 2H), 3.03 (s, 2H), 2.96 (d, J = 17.3 Hz, 1H), 2.54 (dd, J = 15.5, 11.2 Hz, 1H), 2.32 (d, J = 17.3 Hz, 1H), 2.28 (s, 3H), 1.97–1.89 (m, 2H), 1.77–1.56 (m, 6H, containing s at 1.75), 1.53–1.47 (m, 2H), 1.32 (dd, J = 15.6, 2.6 Hz, 1H), 1.18 (s, 3H), 1.12 (s, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.67 (s, 3H), 0.12 (s, 3H), 0.01 (s, 3H); ^{13}C

NMR (150 MHz, $CDCl_3$) δ 209.5 (s), 155.6 (s), 150.4 (s), 134.6 (s), 131.8 (s), 130.3 (s), 128.0 (d), 113.8 (d), 112.8 (d), 77.3 (d), 60.4 (q), 56.2 (t), 55.6 (d), 55.4 (q), 53.2 (t), 51.8 (s), 47.5 (s), 43.7 (s), 40.3 (t), 36.5 (t), 33.8 (t), 32.2 (q), 28.6 (t), 25.8 (q, 3C), 23.9 (q), 22.6 (t), 22.5 (q), 18.6 (q), 17.9 (s), 16.6 (q), 16.4 (q), −4.8 (q), −4.9 (q); IR (neat) 1710, 1600, 1250, 1220, 1060, 830, 770 cm^{-1}; MS *m/e* (rel intensity) 570 (M^+, 64), 513 (100), 177 (83); HRMS calcd for $C_{35}H_{58}O_4Si$ 570.4105, found 570.4124.

Reduction of 51. To a solution of **51** (5.70 g, 10.0 mmol) in MeOH (120 mL) was added $NaBH_4$ (0.91 g, 24.0 mmol) at rt. The mixture was stirred at rt for 12 h, and then $NaBH_4$ (378 mg, 10.0 mol) was added. The mixture was stirred at rt for 7 h, and more $NaBH_4$ (378 mg, 10.0 mol) was added. After the mixture was stirred for another 4 h, water was added. The mixture was extracted with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). Similar reaction was undertaken using 4.17 g (7.31 mmol) of **51**. The combined crude products were chromatographed on SiO_2 (elution with ether/hexane, 5:95 to 10:90) gave **52** (5.16 g, 52%) and **53** (3.39 g, 34%) as a colorless oil, respectively. **52**: ^1H NMR (600 MHz, $CDCl_3$) δ 6.57 (d, *J* = 3.0 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 5.42 (t, *J* = 7.1 Hz, 1H), 3.87 (m, 1H), 3.77−3.74 (m, 4H, containing s at 3.75), 3.69 (s, 3H), 3.40 (dd, *J* = 15.5, 7.3 Hz, 1H), 3.35 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.28 (s, 3H), 2.26−2.18 (m, 2H), 2.12 (dd, *J* = 13.2, 9.4 Hz, 1H), 1.98−1.92 (m, 3H), 1.80−1.46 (m, 9H, containing s at 1.80), 1.27−1.18 (m, 5H, containing s at 1.18), 1.15 (s, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.69 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6 (s), 150.5 (s), 134.8 (s), 132.9 (s), 131.9 (s), 127.3 (d), 114.0 (d), 112.8 (d), 77.5 (d), 67.0 (d), 60.4 (q), 55.6 (d), 55.4 (q), 52.0 (s), 50.6 (t), 48.7 (t), 47.6 (s), 44.2 (s), 39.8 (t), 36.8 (t), 33.9 (t), 32.3 (q), 28.9 (t), 25.9 (q, 3C), 25.2 (q), 22.8 (t), 22.5 (q), 18.5 (q), 18.0 (s), 16.42 (q), 16.39 (q), −4.7 (q), −4.9 (q); IR (neat) 3350, 1600, 1250, 1220, 1060, 830, 770 cm^{-1}; MS *m/e* (rel intensity) 572 (M^+, trace), 220 (100); HRMS calcd for $C_{35}H_{60}O_4$ 572.4261, found 572.4244. **53**: ^1H NMR (600 MHz, $CDCl_3$) δ 6.57 (d, *J* = 3.0 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 5.42 (t, *J* = 7.1 Hz, 1H), 3.80 (m, 1H), 3.75−3.70 (m, 4H, containing s at 3.75), 3.69 (s, 3H), 3.43−3.33 (m, 2H), 2.85 (dd, *J* = 14.8, 11.3 Hz, 1H), 2.28 (s, 3H), 2.16−2.08 (m, 2H), 2.04 (dd, *J* = 14.8, 6.8 Hz, 1H), 2.01−1.92 (m, 2H), 1.81−1.46 (m, 9H, containing s at 1.79), 1.29−1.09 (m, 8H, containing s at 1.18 and s at 1.09), 0.98 (s, 3H), 0.88 (s, 9H), 0.67 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7 (s), 150.5 (s), 134.8 (s), 132.8 (s), 131.9 (s), 127.4 (d), 113.9 (d), 112.9 (d), 77.7 (d), 67.4 (d), 60.5 (q), 55.6 (d), 55.4 (q), 51.7 (s), 50.7 (t), 49.0 (t), 47.7 (s), 44.1 (s), 39.3 (t), 37.1 (t), 34.2 (t), 32.2 (q), 28.9 (t), 25.9 (q, 3C), 25.0 (q), 23.1 (t), 22.4 (q), 18.3 (q), 18.0 (s), 16.4 (q), 16.3 (q), −4.7 (q), −4.8 (q); IR (neat) 3350, 1600, 1245, 1215, 1060, 1030, 830, 770 cm^{-1}; MS *m/e* (rel intensity) 572 (M^+, trace), 220 (100); HRMS calcd for $C_{35}H_{60}O_4$ 572.4261, found 572.4244.

Esterification of 52 with PvCl. To a solution of **52** (5.16 g, 9.01 mmol) and DMAP (55 mg, 0.45 mmol) in dry pyridine (70 mL) was added PvCl (3.33 mL, 27.1 mmol) at 0 °C. The mixture was stirred at rt for 1 day, and more DMAP (25 mg) and PvCl (0.33 mL, 0.27 mmol) were added. After the mixture was stirred at rt for 5 h, water was added. The mixture was extracted with ether. The combined extracts were washed successively with 3% HCl, saturated aqueous $CuSO_4$, water, and brine and dried ($MgSO_4$). Evaporation of the solvent followed by rapid column chromatography on SiO_2 (elution with ether/hexane, 1:99) gave the ester **54** (6.50 g, ~100%) containing a small amount of impurity. An analytical sample was obtained by flash chromatography of a small sample on SiO_2 (elution with ether/hexane, 2:98). **54**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, *J* = 3.0 Hz, 1H), 6.52 (d, *J* = 3.0 Hz, 1H), 5.32 (t, *J* = 6.9 Hz, 1H), 5.12 (m, 1H), 3.76−3.71 (m, 4H, containing s at 3.74), 3.67 (s, 3H), 3.36−3.26 (m 2H), 2.31−2.24 (m, 4H, containing s at 2.28), 2.13−2.01 (m, 3H), 1.96−1.87 (m, 2H), 1.82 (s, 3H), 1.75−1.66 (m, 2H), 1.54−1.44 (m, 2H), 1.36 (dd, *J* = 15.1, 8.1, Hz, 1H), 1.32−1.25 (m, 1H), 1.23−1.10 (m, 13H, containing s at 1.16), 0.97 (s, 3H), 0.90 (s, 3H), 0.88 (s, 9H), 0.67 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR(150 MHz, $CDCl_3$) δ 177.8 (s), 155.5 (s), 150.4 (s), 134.9 (s), 132.0 (s), 131.8 (s), 127.1 (d), 113.7 (d), 112.9 (d), 77.1 (d), 70.7 (d), 60.5 (q), 55.38 (d or q), 55.35 (q or d), 51.9 (s), 47.5 (s + t), 45.0 (t), 43.8 (s), 39.6 (t), 38.5 (s), 36.7 (t), 33.6 (t), 32.0 (q), 28.6 (t), 27.1 (q, 3C), 25.9 (q, 3C), 25.0 (q), 22.6 (t + q), 18.6 (q), 17.9 (s), 16.5 (q), 16.4 (q), −4.7 (q), −4.8 (q); IR (neat) 1720, 1600, 1160, 1060, 835, 770 cm^{-1}; MS *m/e* (rel intensity) 656 (M^+, 21), 599 (100), 177 (94); HRMS calcd for $C_{40}H_{68}O_5Si$ 656.4836, found 656.4828.

Selective Deprotection of TBDMS Group in 54. A solution of the above ester **54** (6.49 g, ~9.8 mmol) in AcOH (155 mL), THF (55 mL), and water (55 mL) was stirred at 50 °C for 1 day. The cooled mixture was neutralized by aqueous NaOH, and the mixture was extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave the crude alcohol **55**. An analytical sample was obtained by flash chromatography of a small sample on SiO_2 (elution with ether/hexane, 30:70). **55**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, *J* = 3.0 Hz, 1H), 6.52 (d, *J* = 3.0 Hz, 1H), 5.33 (t, *J* = 6.9 Hz, 1H), 5.08 (m, 1H), 3.79 (m, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.32 (dd, *J* = 15.3, 7.2 Hz, 1H), 3.28 (dd, *J* = 15.3, 7.3 Hz, 1H), 2.28−2.25 (m, 4H, containing s at 2.28), 2.14 (dd, *J* = 15.1, 11.2 Hz, 1H), 2.10−2.02 (m, 3H, containing dd, *J* = 13.1, 7.8 Hz at 2.09), 1.89 (m, 1H), 1.83 (s, 3H), 1.77 (s, 3H), 1.69−1.50 (m, 3H), 1.36 (dd, *J* = 15.2, 8.0 Hz, 1H), 1.23−1.14 (m, 13H, containing s at 1.18 and s at 1.16), 0.95 (s, 3H), 0.87 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9 (s), 155.5 (s), 150.5 (s), 134.9 (s), 131.9 (s), 131.8 (s), 127.2 (d), 113.8 (d), 113.0 (d), 77.6 (d), 70.8 (d), 60.5 (q), 55.43 (d or q), 55.41 (q or d), 51.9 (s), 47.3 (t), 47.2 (s), 44.5 (t), 43.8 (s), 40.1 (t), 38.5 (s), 36.8 (t), 33.1 (t), 32.0 (q), 28.7 (t), 27.1 (q, 3C), 24.4 (q), 22.8 (t), 22.4 (q), 18.2 (q), 16.5 (q), 16.4 (q); IR (neat) 3350, 1720, 1600, 1285, 1220, 1160, 1060, 1010, 855 cm^{-1}; MS *m/e* (rel intensity) 542 (M^+, 42), 440 (50), 177 (100); HRMS calcd for $C_{34}H_{54}O_5$ 542.3971, found 542.3979.

Oxidation of 55. Reaction of the above alcohol **55** with PCC as described for the preparation of **43** gave the ketone **6** (3.61 g, 74% from **52**) after column chromatography on SiO_2 (elution with ether/hexane, 20:80). **6**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, *J* = 3.0 Hz, 1H), 6.50 (d, *J* = 3.0 Hz, 1H), 5.33 (t, *J* = 7.0 Hz, 1H), 5.09 (m, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.33−3.26 (m, 2H), 2.60−2.55 (m, 2H), 2.45 (m, 1H), 2.34−2.28 (m, 4H, containing s at 2.28), 2.14−2.07 (m, 2H), 1.82 (s, 3H), 1.73−1.64 (m, 3H), 1.46 (dd, *J* = 15.2, 8.1 Hz, 1H), 1.21 (s, 3H), 1.16 (s, 9H), 1.09 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.4 (s), 177.8 (s), 155.5 (s), 150.4 (s), 134.7 (s), 131.8 (s), 131.7 (s), 127.4 (d), 113.6 (d), 112.9 (d), 70.4 (d), 64.5 (d), 60.5 (q), 55.4 (q), 52.5 (s), 47.2 (t), 46.1 (s), 45.8 (s), 44.4 (t), 40.1 (t), 38.5 (s), 36.8 (t), 35.8 (t), 30.4 (q), 28.7 (t), 27.1 (q, 3C), 24.0 (q), 23.0 (q), 21.7 (t), 18.6 (q), 16.6 (q), 16.4 (q); IR (neat) 1720, 1690, 1600, 1280, 1220, 1160, 1060, 1010, 850 cm^{-1}; MS *m/e* (rel intensity) 540 (M^+, 100), 438 (83), 193 (81), 165 (71); HRMS calcd for $C_{34}H_{52}O_5$ 540.3815, found 540.3797.

Preparation of Enone 56. Reaction of **6** (3.59 g, 6.64 mmol) with TMSOTf as described for the preparation of **40** gave the silyl enol ether (3.88 g, 95%) after column chromatography on SiO_2 (elution with ether/hexane, 5:95). **Silyl enol ether of 6**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, *J* = 3.1 Hz, 1H), 6.50 (d, *J* = 3.1 Hz, 1H), 5.32 (t, *J* = 6.9 Hz, 1H), 5.07 (m, 1H), 4.69 (m, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.33 (dd, *J* = 15.6, 7.4 Hz, 1H), 3.29 (dd, *J* = 15.6, 7.0 Hz, 1H), 2.39−2.26 (m, 5H, containing s at 2.28), 2.14−2.07 (m, 4H), 1.95 (d, *J* = 14.7 Hz, 1H), 1.83 (s, 3H), 1.62 (d, *J* = 12.0 Hz, 1H), 1.57−1.47 (m, 3H), 1.16 (s, 9H), 1.01 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H), 0.72 (s, 3H), 0.18 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.8 (s), 155.7 (s), 155.6 (s), 150.4 (s), 134.8 (s), 132.1 (s), 131.8 (s), 127.1 (d), 113.7 (d), 112.9 (d), 103.7 (d), 70.9 (d), 60.5 (q), 55.9 (d), 55.4 (q), 52.1 (s), 47.4 (t), 46.7 (s), 45.3 (t), 44.7 (s), 42.1 (t), 38.5 (s), 34.4 (t), 28.9 (t), 28.7 (q), 27.1 (q, 3C), 24.6 (t), 24.2 (q), 23.2 (q), 20.4 (q), 16.41 (q), 16.39 (q), 0.54 (q, 3C); IR (neat) 1720, 1670, 1600, 1250, 1215, 1160, 1060, 840 cm^{-1}. Reaction of the above enol ether (2.50 g, 4.23 mmol) with $Pd(OAc)_2$ as described for the preparation of **40** gave the enone **56** (1.84 g, 81%) after column chromatography on SiO_2 (elution with ether/hexane, 2:98). **56**: colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, *J* = 2.9 Hz, 1H), 6.50 (d, *J* = 2.9

Hz, 1H), 6.36 (ddd, J = 12.1, 6.4, 2.4 Hz, 1H), 5.86 (d, J = 12.5 Hz, 1H), 5.33 (t, J = 7.1 Hz, 1H), 5.00 (dd, J = 13.0, 7.9 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.33 (dd, J = 15.4, 7.5 Hz, 1H), 3.27 (dd, J = 15.4, 6.8 Hz, 1H), 2.60 (d, J = 9.8 Hz, 1H), 2.39 (dd, J = 20.0 Hz, 6.5 Hz, 1H), 2.31–2.24 (m, 4H, containing s at 2.28), 2.19 (br d, J = 20.2 Hz, 1H), 2.11–2.04 (m, 2H), 1.95 (d, J = 14.8 Hz, 1H), 1.83 (s, 3H), 1.63 (d, J = 14.6 Hz, 1H), 1.56 (dd, J = 14.9, 7.3 Hz, 1H), 1.14 (s, 9H), 1.01 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.8 (s), 177.7 (s), 155.5 (s), 150.4 (s), 145.0 (d), 134.7 (s), 131.8 (s), 131.7 (s), 129.4 (d), 127.5 (d), 113.7 (d), 113.0 (d), 70.4 (d), 63.7 (d), 60.5 (q), 55.4 (q), 52.4 (s), 47.3 (t), 46.1 (s), 45.8 (s), 45.5 (t), 42.4 (t), 40.4 (t), 38.5 (s), 28.7 (t), 28.0 (q), 27.0 (q, 3C), 25.7 (q), 22.1 (q), 19.8 (q), 16.42 (q), 16.40 (q); IR (neat) 1720, 1660, 1600, 1290, 1230, 1160, 1010, 840 cm^{-1}; MS m/e (rel intensity) 538 (M^+, 100), 436 (67), 165 (74); HRMS calcd for $C_{34}H_{50}O_5$ 538.3658, found 538.3646.

Epoxidation of 56. Reaction of **56** (364 mg, 0.68 mmol) with 30% aqueous H_2O_2 and 6 N NaOH was undertaken at 30 °C for 2 days as described for the preparation of **41**. To complete this reaction, more 30% aqueous H_2O_2 (0.69 mL, 6.8 mmol) was added, and the mixture was stirred for another 1 day. This operation was repeated once more. After workup, the crude product **57** was obtained. An analytical sample was obtained by flash chromatography of a small sample on SiO_2 (elution with ether/hexane, 15:85). **57**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (d, J = 2.8 Hz, 1H), 6.49 (d, J = 2.8 Hz, 1H), 5.35 (t, J = 7.1 Hz, 1H), 5.05 (m, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 3.34–3.23 (m, 3H), 3.16 (m, 1H), 2.57 (br d, J = 8.4 Hz, 1H), 2.31–2.26 (m, 4H containing s at 2.27), 2.16–2.00 (m, 4H), 1.98 (d, J = 15.0 Hz, 1H), 1.83 (s, 3H), 1.67 (d, J = 15.7 Hz, 1H), 1.57 (dd, J = 15.1, 7.6 Hz, 1H), 1.17 (s, 9H), 1.15 (s, 3H), 0.934 (s, 3H), 0.929 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7 (s), 177.8 (s), 155.5 (s), 150.3 (s), 134.6 (s), 131.8 (s), 131.5 (s), 127.7 (d), 113.5 (d), 113.1 (d), 70.4 (d), 64.5 (d), 60.5 (q), 55.5 (d), 55.3 (q), 54.8 (d), 53.6 (s), 48.4 (s), 47.2 (t), 45.7 (s), 44.7 (t), 38.5 (s), 37.6 (t), 37.4 (t), 29.4 (q), 28.7 (t), 27.0 (q, 3C), 26.5 (q), 23.7 (q), 19.7 (q), 16.5 (q), 16.4 (q); IR (neat) 1720, 1590, 1280, 1220, 1160, 1060, 1010 cm^{-1}; MS m/e (rel intensity) 554 (M^+, 78), 452 (71), 165 (100), 57 (50); HRMS calcd for $C_{34}H_{50}O_6$ 554.3607, found 554.3622.

Reduction of 57 with $LiAlH_4$. Reaction of the above epoxide **57** with $LiAlH_4$ (128 mg, 3.38 mmol) at 0 °C as described for the preparation of **17** and **18** gave the epoxy diol **58** (242 mg, 76% from **56**) as a colorless oil after column chromatography on SiO_2 (elution with ether/hexane, 70:30): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 (d, J = 2.8 Hz, 1H), 6.53 (d, J = 2.9 Hz, 1H), 5.41 (t, J = 7.1 Hz, 1H), 4.07 (br s, 1H), 3.82 (m, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.42–3.30 (m, 4H), 2.27 (s, 3H), 2.24 (br s, 1H), 2.21–2.10 (m, 4H), 2.07 (dd, J = 10.1, 3.7 Hz, 1H), 1.96 (dd, J = 16.6, 7.5 Hz, 1H), 1.79–1.75 (m, 5H containing s at 1.79), 1.38 (dd, J = 14.7, 6.5 Hz, 1H), 1.15 (s, 3H), 1.14–1.11 (m, 4H containing s at 1.13), 0.94 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6 (s), 150.4 (s), 134.6 (s), 132.5 (s), 131.9 (s), 127.6 (d), 113.8 (d), 112.8 (d), 74.5 (d), 66.8 (d), 61.5 (d), 60.4 (q), 57.8 (d), 55.4 (q), 53.6 (d), 53.2 (s), 50.8 (t), 49.4 (t), 46.9 (s), 44.2 (s), 40.9 (t), 37.3 (t), 30.3 (q), 28.9 (t), 26.7 (q), 22.7 (q), 19.6 (q), 16.4 (q, 2C); IR (neat) 3450, 1600, 1220, 1060, 1010 cm^{-1}; MS m/e (rel intensity) 472 (M^+, 8), 220 (100); HRMS calcd for $C_{29}H_{44}O_5$ 472.3189, found 472.3206.

Reduction of 58 with DIBALH. Reaction of **58** (142 mg, 0.30 mmol) with DIBALH (1.5 M toluene solution, 4.00 mL, 6.00 mmol) was undertaken at rt for 4 h as described for the preparation of **26**. To complete this reaction, more DIBALH (0.40 mL, 0.60 mmol) was added, and the mixture was stirred for another 4 h. Addition of 3% aqueous tartaric acid followed by workup and column chromatography on SiO_2 (elution with ether/hexane, 80:20) gave the triol **59** (78 mg, 53%) as a waxy white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (d, J = 2.8 Hz, 1H), 6.53 (d, J = 2.8 Hz, 1H), 5.43 (t, J = 7.3 Hz, 1H), 4.16 (m, 1H), 3.87 (m, 1H), 3.80 (m, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.40 (dd, J = 15.6, 7.3 Hz, 1H), 3.37 (dd, J = 15.6, 7.3 Hz, 1H), 2.28 (s, 3H), 2.19–2.14 (m, 2H), 2.11 (dd, J = 9.8, 5.9 Hz, 1H), 2.05 (m, 1H), 2.02 (dd, J = 14.4, 10.4 Hz, 1H), 1.84 (d, J = 14.4 Hz, 1H), 1.79 (s, 3H), 1.79–1.65 (m, 5H), 1.40–1.25 (m, 2H), 1.21 (m, 1H), 1.20 (s, 3H), 1.18 (s, 3H), 0.98 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6 (s), 150.4 (s), 134.7 (s), 132.6 (s), 132.0 (s), 127.5 (d), 113.8 (d), 112.8 (d), 78.0 (d), 69.0 (d), 67.1 (d), 60.5 (q), 55.4 (q), 52.3 (s), 51.3 (t), 51.0 (t), 50.7 (d), 47.6 (s), 44.7 (s), 38.5 (t), 33.0 (t), 30.3 (q), 29.5 (t), 28.9 (t), 25.9 (q), 23.0 (q), 20.5 (q), 16.41 (q), 16.39 (q); IR (neat) 3400, 1600, 1220 1060, 1010 cm^{-1}; MS m/e (rel intensity) 474 (M^+, 5), 220 (100); HRMS calcd for $C_{29}H_{46}O_5$ 474.3345, found 474.3340.

Esterification of 59 with *m*-Bromobenzoyl Chloride. To a solution of **59** (6 mg, 0.01 mmol) in dry pyridine (1.5 mL) was added *m*-bromobenzoyl chloride (9 μL, 0.007 mmol) at rt. After the mixture was stirred for 40 min, 10% aqueous HCl was added to the cooled mixture. The mixture was extracted with ether, and the combined extracts were washed with 1 N NaOH and brine and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography on SiO_2 (elution with ether/hexane, 50:50) gave the ester **60** (8 mg, 96%): white solid recrystallized from ether/hexane: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (m, 1H), 7.97 (m, 1H), 7.70, (m, 1H), 7.34 (t, J = 7.8 Hz, 1H), 6.58 (d, J = 2.9 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 5.64 (m, 1H), 5.42 (t, J = 7.3 Hz, 1H), 4.07 (m, 1H), 3.84 (m, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.38 (m, 2H), 2.36 (m, 1H), 2.28 (s, 3H), 2.23–1.81 (m, 4H), 1.57 (s, 2H), 1.80 (s, 3H), 1.45–1.27 (m, 9H, containing s at 1.33), 1.26 (s, 3H), 1.01 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 164.3 (s), 155.6 (s), 150.4 (s), 136.0 (d), 134.7 (s), 132.6 (s), 132.5 (d), 132.3 (s), 132.0 (s), 130.0 (d), 128.2 (d), 127.6 (d), 122.5 (s), 113.9 (d), 112.8 (d), 76.2 (d), 74.2 (d), 67.1 (d), 60.5 (q), 55.4 (q), 52.3 (s), 51.4 (t), 51.0 (t), 50.5 (d), 47.8 (s), 44.8 (s), 38.5 (t), 32.7 (t), 30.2 (q), 29.0 (t), 25.8 (q), 25.2 (t), 23.2 (q), 20.6 (q), 16.42 (q), 16.36 (q); IR (KBr) 3400, 1720, 1600, 1580, 1290, 1260, 760 cm^{-1}; MS m/e (rel intensity) 658 (M^+ + 2, trace), 656 (M^+, trace), 220 (100); HRMS calcd for $C_{36}H_{49}BrO_6$ 656.2712, found 656.2710.

Reduction of 58 with $LiBEt_3H$. To a solution of the epoxy alcohol **58** (235 mg, 0.50 mmol) in THF (10 mL) was added $LiBEt_3H$ (1.0 M solution in THF, 2.49 mL, 2.49 mmol) at rt under argon. After the mixture was stirred at 65 °C for 2 days, more $LiBEt_3H$ (2.49 mL) was added. The mixture stirred at 65 °C for another 2 days, and saturated aqueous K_2CO_3 was added. The mixture was extracted with ether, and the combined extracts were dried (Na_2SO_4). Evaporation of the solvent followed by column chromatography on SiO_2 (elution with MeOH/ether, 2:98 to 10:90) gave the recovered **58** (46 mg) and the triol **61** (156 mg, 66%) as a waxy white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (d, J = 2.8 Hz, 1H), 6.53 (d, J = 2.8 Hz, 1H), 5.41 (t, J = 7.1 Hz, 1H), 4.12 (m, 1H), 3.90–3.80 (m, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 3.40 (dd, J = 15.5, 7.1 Hz, 1H), 3.33 (dd, J = 15.5, 7.1 Hz, 1H), 2.37 (dd, J = 15.4, 11.4 Hz, 1H), 2.32 (m, 1H), 2.28 (s, 3H), 2.17 (dd, J = 13.0, 4.0 Hz, 1H), 2.12 (dd, J = 13.0, 8.9 Hz, 1H), 2.00 (dd, J = 12.8, 9.6 Hz, 1H), 1.98–1.93 (m, 2H), 1.79 (s, 3H), 1.75 (m, 1H), 1.72 (s, 1H), 1.63 (dd, J = 14.1, 11.4 Hz, 1H), 1.52 (s, 1H), 1.33 (s, 1H), 1.24 (s, 3H), 1.20 (m, 1H), 1.19 (s, 3H), 1.07 (dd, J = 15.4, 3.1 Hz, 1H), 0.97 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5 (s), 150.4 (s), 134.7 (s), 132.5 (s), 132.0 (s), 127.5 (d), 113.8 (d), 112.9 (d), 74.6 (d), 66.8 (d), 66.7 (d), 60.5 (q), 55.4 (d), 55.3 (q), 51.0 (s), 50.4 (t), 47.2 (t), 47.0 (t), 46.6 (s), 43.9 (s), 42.8 (t), 39.2 (t), 32.1 (q), 29.0 (t), 25.0 (q), 22.3 (q), 17.6 (q), 16.43 (q), 16.41 (q); IR (neat) 3300, 1600, 1200, 1060, 740 cm^{-1}; MS m/e (rel intensity) 474 (M^+, 8), 220 (100); HRMS calcd for $C_{29}H_{46}O_5$ 474.3345, found 474.3353.

Oxidation of 61. To a solution of Dess–Martin periodinane[27] (80 wt %, 85 mg, 0.16 mmol) in dry CH_2Cl_2 (1.0 mL) was added a solution of **61** (19 mg, 2.5 mmol) in dry CH_2Cl_2 (2.5 mL) at rt under argon. After stirring at rt for 40 min, the mixture was diluted with ether and saturated aqueous $NaHCO_3$ containing 20% aqueous $Na_2S_2O_3$. The mixture was stirred for another 1 h. The mixture was extracted with ether, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent followed by column chromatography on SiO_2 (elution with ether) gave the triketone **62** (9.2 mg, 48%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (d, J = 3.0 Hz, 1H), 6.55 (d, J = 3.0 Hz, 1H), 5.45 (t, J = 7.1 Hz, 1H), 3.98 (d, J =

17.5 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.42 (d, J = 17.5 Hz, 1H), 3.39 (d, J = 7.1 Hz, 2H), 3.05 (s, 2H), 2.89 (d, J = 17.6 Hz, 1H), 2.72 (d, J = 9.6 Hz, 1H), 2.69 (d, J = 18.4 Hz, 1H), 2.64 (dd, J = 16.4, 9.6 Hz, 1H), 2.60 (d, J = 17.6 Hz, 1H), 2.48 (d, J = 18.4 Hz, 1H), 2.28 (s, 3H), 1.96 (dd, J = 1.3, 16.4 Hz, 1H), 1.75 (s, 3H), 1.22 (s, 3H), 1.12 (s, 3H), 0.99 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.9 (s), 206.1 (s), 203.9 (s), 155.6 (s), 150.3 (s), 134.4 (s), 131.9 (s), 129.7 (s), 128.6 (d), 113.6 (d), 113.0 (d), 64.3 (d), 60.5 (q), 58.1 (t), 55.9 (t), 55.4 (q), 54.1 (t), 52.6 (t), 52.5 (s), 47.6 (s), 45.8 (s), 38.3 (t), 29.2 (q), 28.8 (t), 24.9 (q), 23.4 (q), 19.3 (q), 16.6 (q), 16.4 (q); IR (neat) 1710, 1600, 1170, 1060, 1010, 730 cm^{-1}; MS m/e (rel intensity) 468 (M^+, 100), 165 (50); HRMS calcd for $C_{29}H_{40}O_5$ 468.2876, found 468.2865.

Methylation of 62 with MeI–K_2CO_3. Reaction of **62** (7.0 mg, 0.015 mmol) with MeI (0.07 mL) and K_2CO_3 (35 mg) as described for the reaction of **43** gave the monomethylated enones **64** (2.4 mg, 33%) and **65** (1.5 mg, 20%) and *C*-methylated compound (<1 mg) after column chromatography on SiO_2 (elution with ether/hexane, 50:50). **64**: colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.58 (d, J = 2.9 Hz, 1H), 6.56 (d, J = 2.9 Hz, 1H), 5.43 (t, J = 7.3 Hz, 1H), 5.35 (s, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.61 (s, 3H), 3.39 (d, J = 7.3 Hz, 2H), 3.04 (s, 2H), 2.79 (d, J = 17.7 Hz, 1H), 2.64 (d, J = 10.1 Hz, 1H), 2.53 (d, J = 17.7 Hz, 1H), 2.45 (dd, J = 10.1, 15.1 Hz, 1H), 2.33 (s, 2H), 2.29 (s, 3H), 1.88 (d, J = 15.1 Hz, 1H), 1.74 (s, 3H), 1.14 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 208.0 (s), 203.7 (s), 172.2 (s), 155.6 (s), 150.3 (s), 134.5 (s), 131.9 (s), 130.0 (s), 128.3 (d), 113.7 (d), 112.9 (d), 103.5 (d), 64.1 (d), 60.5 (q), 55.9 (t), 55.6 (q), 55.4 (q), 53.4 (t), 51.0 (s), 46.1 (s), 45.3 (s), 44.6 (t), 41.5 (t), 28.7 (t), 28.0 (q), 24.6 (q), 22.2 (q), 19.9 (q), 16.5 (q), 16.4 (q); IR (neat) 1710, 1620, 1380, 1210, 1160, 1060, 1010 cm^{-1}; MS m/e (rel intensity) 482 (M^+, 100); HRMS calcd for $C_{30}H_{42}O_5$ 482.3032, found 482.3056. **65**: colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.58 (d, J = 2.9 Hz, 1H), 6.56 (d, J = 2.9 Hz, 1H), 5.43 (t, J = 7.1 Hz, 1H), 5.39 (s, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.62 (s, 3H), 3.39 (d, J = 7.1 Hz, 2H), 3.04 (s, 2H), 2.70 (d, J = 17.7 Hz, 1H), 2.62–2.45 (m, 4H), 2.37 (d, J = 19.5 Hz, 1H), 2.29 (s, 3H), 1.92 (d, J = 13.7 Hz, 1H), 1.74 (s, 3H), 1.08 (s, 6H), 1.05 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 208.2 (s), 200.2 (s), 179.2 (s), 155.5 (s), 150.3 (s), 134.5 (s), 131.9 (s), 130.0 (s), 128.3 (d), 113.6 (d), 112.9 (d), 103.8 (d), 60.5 (q), 56.6 (d), 56.0 (q), 55.8 (t), 55.4 (q), 53.8 (t), 52.4 (t), 49.9 (s), 46.5 (s), 44.9 (s), 44.5 (t), 28.7 (t), 27.3 (q), 25.8 (q), 22.0 (q), 20.2 (q), 16.5 (q), 16.4 (q); IR (neat) 1710, 1620, 1390, 1220, 1150, 1060, 1010 cm^{-1}; MS m/e (rel intensity) 482 (M^+, 100), 221 (97); HRMS calcd for $C_{30}H_{42}O_5$ 482.3032, found 482.3012. ***C*-Methylated compound**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.58 (d, J = 2.9 Hz, 1H), 6.57 (d, J = 2.9 Hz, 1H), 5.42 (t, J = 7.6 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.39 (d, J = 7.6 Hz, 2H), 3.04 (s, 2H), 2.83–2.31 (m, 6H), 2.29 (s, 3H), 1.87 (d, J = 13.7 Hz, 1H), 1.76 (s, 3H), 1.74 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.86 (s, 3H); MS m/e (rel intensity) 496 (M^+, 100); HRMS calcd for $C_{31}H_{44}O_5$ 496.3189, found 496.3181.

Methylation of 62 with Me_3OBF_4–Proton Sponge. Reaction of **62** (6.2 mg, 0.013 mmol) with Me_3OBF_4 (10 mg, 0.065 mmol) and Proton Sponge (18 mg, 0.078 mmol) at rt as described for the preparation of **49** gave a product containing a 1:1 mixture of **64** and **65** and Proton Sponge. In this case, water was added to quench the reaction instead of saturated aqueous $NaHCO_3$, and the organic extracts were not washed with aqueous oxalic acid. To a solution of this crude mixture in dry CH_2Cl_2 (2.0 mL) were added again Me_3OBF_4 (19 mg, 0.12 mmol) and Proton Sponge (37 mg, 0.16 mmol). The mixture was stirred under argon at 40 °C for 4 h and diluted with ether and saturated aqueous $NaHCO_3$. The mixture was extracted with ether, and the combined organic extracts were washed with 5% aqueous citric acid and saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography on SiO_2 (elution with ether/hexane, 60:40) gave the tetramethyl ether **2** (3 mg, 46%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 2H), 5.41 (t, J = 7.2 Hz, 1H), 4.70 (br s, 1H), 3.97 (d, J = 1.6 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 3.51 (s, 3H), 3.48 (s, 3H), 3.39 (d, J = 7.2 Hz, 2H), 3.04 (s, 2H), 2.70 (d, J = 16.6 Hz, 1H), 2.48 (d, J = 16.6 Hz, 1H), 2.44 (dd, J = 8.9, 14.6 Hz, 1H), 2.29 (s, 3H), 2.13 (d, J = 8.9 Hz, 1H), 1.95 (d, J = 14.5 Hz, 1H), 1.73 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H); ^{1}H NMR (270 MHz, C_6D_6) δ 6.80 (d, J = 3.0 Hz, 1H), 6.61 (d, J = 3.0 Hz, 1H), 5.43 (t, J = 7.2 Hz, 1H), 4.98 (t, J = 1.8 Hz, 1H), 4.02 (d, J = 1.8 Hz, 1H), 3.45 (s, 6H), 3.43 (d, J = 7.2 Hz, 2H), 3.32 (s, 3H), 3.10 (s, 3H), 2.80 (s, 2H), 2.62 (dd, J = 14.6, 9.6 Hz, 1H), 2.57 (d, J = 17.0 Hz, 1H), 2.37 (br d, J = 9.0 Hz, 1H), 2.36 (d, J = 17.0 Hz, 1H), 2.31 (d, J = 14.6 Hz, 1H), 2.21 (s, 3H), 1.70 (s, 3H), 1.42 (s, 3H), 1.27 (s, 3H), 1.01 (s, 3H), 0.88 (s, 3H); IR (neat) 2900, 1710, 1600, 1480, 1210, 1160 cm^{-1}; MS m/e 496 (M^+, 10), 482 (5), 235 (10), 194 (63), 179 (100); HRMS calcd for $C_{31}H_{44}O_5$ 496.3188, found 496.3193.

Preparation of Model Compounds 63 and 66. (1*R,2*R**,6*R**,7*R**)-7-Allyl-6,7,9,9-tetramethylbicyclo[4.2.1]nonan-2-ol (67).** Deprotection of the TBDMS group of **28** (1.49 g, 4.26 mmol) as described for the preparation of **55** gave **67** (1.01 g, 100%) after flash chromatography on SiO_2 (elution with ether/hexane, 10:90). **67**: white solid; mp 48–50 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.05 (m, 1H), 5.00 (m, 1H), 3.81 (m, 1H), 2.53 (dd, J = 14.1, 7.9 Hz, 1H), 2.42 (dd, J = 15.1, 11.2 Hz, 1H), 2.10 (m, 1H), 1.99 (dd, J = 11.2, 2.6 Hz, 1H), 1.86 (dd, J = 14.1, 6.5 Hz, 1H), 1.78 (m, 1H), 1.73–1.66 (m, 2H), 1.58-1.48 (m, 3H), 1.23 (s, 3H), 1.08 (s, 3H), 1.06 (dd, J = 12.4, 2.8 Hz, 1H), 1.02 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.2 (d), 116.7 (t), 77.9 (d), 55.6 (d), 51.5 (s), 47.5 (s), 46.2 (t), 43.8 (s), 39.6 (t), 37.0 (t), 33.4 (t), 32.3 (q), 24.1 (q), 22.8 (t), 22.4 (q), 18.2 (q); IR (KBr) 3330, 1630, 1370, 1000, 900 cm^{-1}; MS m/e (rel intensity) 177 (M^+ – 59, 100).

(1*R,6*R**,7*R**)-7-Allyl-6,7,9,9-tetramethylbicyclo[4.2.1]nonan-2-one (68).** PCC oxidation of **67** (1.12 g, 4.73 mmol) as described for the preparation of **6** gave **68** (0.96 g, 87%) after column chromatography on SiO_2 (elution with ether/hexane, 10:90). **68**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.09 (m, 1H), 5.03 (m, 1H), 2.62–2.56 (m, 3H), 2.49 (m, 1H), 2.40 (dd, J = 15.5, 10.7 Hz, 1H), 2.06 (m, 1H), 1.96 (dd, J = 14.1, 6.5 Hz, 1H), 1.77–1.67 (m, 3H), 1.55 (dd, J = 15.7, 2.9 Hz, 1H), 1.142 (s, 3H), 1.135 (s, 3H), 1.06 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.9 (s), 136.3 (d), 117.4 (t), 64.6 (d), 52.1 (s), 46.3 (s), 46.1 (t), 45.9 (s), 40.3 (t), 36.3 (t), 35.9 (t), 30.7 (q), 23.6 (q), 23.0 (q), 21.8 (t), 18.6 (q); IR (neat) 1690, 1630, 1380, 905 cm^{-1}; MS m/e (rel intensity) 234 (M^+, trace), 193 (100), 175 (56), 95 (51); HRMS calcd for $C_{16}H_{26}O$ 234.1984, found 234.1981.

(1*R,6*R**,7*R**)-7-Allyl-6,7,9,9-tetramethylbicyclo[4.2.1]non-3-en-2-one (63).** Reaction of **68** (96 mg, 0.41 mmol) with TMSOTf as described for the preparation of **40** gave the silyl enol ether (117 mg, 93%) after flash chromatography on SiO_2 (elution with ether/hexane, 8:92). **Silyl enol ether of 68**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.06–4.96 (m, 2H), 4.72 (m, 1H), 2.46–2.36 (m, 2H), 2.36 (dd, J = 13.8, 9.3 Hz, 1H), 2.16 –2.09 (m, 2H), 1.99 (dd, J = 13.8, 7.1 Hz, 1H), 1.61–1.48 (m, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 0.76 (s, 3H), 0.17 (s, 9H); IR (neat) 1680, 1630, 1380, 1250, 1190, 1150, 890, 870, 840 cm^{-1}. Reaction of the ether (456 mg, 1.49 mmol) with $Pd(OAc)_2$ as described for the preparation of **40** gave the recovered ether (110 mg) and **63** (131 mg, 38%) after flash chromatography on SiO_2 (elution with ether/hexane, 6:94). **63**: colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.39 (ddd, J = 12.5, 6.5, 2.6 Hz, 1H), 5.89 (d, J = 12.5 Hz, 1H), 5.83 (ddt, J = 17.0 10.0, 7.0 Hz, 1H), 5.08 (m, 1H), 5.04 (m, 1H), 2.66 (d, J = 9.9 Hz, 1H), 2.47–2.40 (m, 2H), 2.37 (dd, J = 15.1, 9.9 Hz, 1H), 2.33 (dd, J = 20.2, 2.6 Hz, 1H), 2.04 (dt, J = 13.7, 7.0 Hz, 1H), 1.50 (d, J = 15.1 Hz, 1H), 1.15 (s, 3H), 1.052 (s, 3H), 1.048 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.1 (s), 145.2 (d), 136.2 (d), 129.5 (d), 117.6 (t), 63.9 (d), 52.1 (s), 47.2 (t), 46.0 (s), 45.9 (s), 42.4 (t), 39.6 (t), 28.3 (q), 25.7 (q), 22.1 (q), 19.7 (q); IR (neat) 1650, 1390, 1375, 1290, 990, 910, 835 cm^{-1}; MS m/e (rel intensity) 232 (M^+, trace), 191 (100), 163 (51), 123 (51), 121(52), 107 (67), 93 (54); HRMS calcd for $C_{16}H_{24}O$ 232.1827, found 232.1822.

(1*R,3*R**,4*R**,6*R**,7*R**)-7-Allyl-3,4-epoxy-6,7,9,9-tetramethylbicyclo[4.2.1]nonan-2-one (66).** Reaction of **63** (96 mg, 0.41 mmol) with 30% aqueous H_2O_2 and 6 N NaOH was undertaken at rt for 3 days as described for the preparation

of **57** to give **66** (31m g, 22%) after column chromatography on SiO_2 (elution with ether/hexane, 5:95). **66**: white solid; mp 68–70 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.1, 10.0, 7.1 Hz, 1H), 5.12 (m, 1H), 5.07 (m, 1H), 3.27 (ddd, J = 7.6, 4.0, 1.1 Hz, 1H), 3.19 (dd, 4.0, 1.5 Hz, 1H), 2.64 (d, J = 9.4 Hz, 1H), 2.45 (dd, J = 13.8, 7.1 Hz, 1H), 2.40 (dd, J = 15.7, 9.4 Hz, 1H), 2.17 (dd, J = 16.5, 0.8 Hz, 1H), 2.08 (dd, J = 16.5, 7.6 Hz, 1H), 2.07 (dd, J = 13.8, 7.1 Hz, 1H), 1.55 (dd, J = 15.7, 1.1 Hz, 1H), 1.13 (s, 3H), 1.11 (s, 3H), 0.97 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.1 (s), 135.8 (d), 118.1 (t), 64.8 (d), 55.6 (d), 54.9 (d), 53.1 (s), 48.7 (s), 46.4 (t), 45.6 (s), 37.4 (t), 36.9 (t), 29.7 (q), 26.4 (q), 23.7 (q), 19.6 (q); IR (KBr) 1700, 1630, 1380, 1375, 1250, 1110, 1090, 990, 900, 810 cm^{-1}; MS m/e (rel intensity) 248 (M^+, 2), 137 (51), 123 (100), 110 (52), 109 (85), 107 (52), 95 (63), 83 (60), 81 (51), 55 (54), 41 (55); HRMS calcd for $C_{16}H_{24}O_2$ 248.1776, found 248.1763. The stereochemistry of the epoxy ring was determined as shown in **66** by the NOE experiment. Irradiation of the C19 methyl protons (δ 1.13) showed NOE enhancements (1% and 8%) of the C12 and C13 α-protons (δ 3.19 and 3.27).[14]

X-ray Analysis of 60.[29] Crystal data: $C_{36}H_{49}BrO_6$, monoclinic $C2/c$, a = 39.783(7) Å, b = 9.670(8) Å, c = 19.292(6) Å, β = 93.02(2)°, V = 7411(6) Å^3, Z = 8. Data were collected at 23 °C on a Rigaku AFC5R diffractometer with graphite monochromated Mo Kα radiation giving 9042 unique reflections. The structure was solved by a direct method (SAPI91) to yield R = 0.101 for 2423 independent reflections with $I > 3\sigma(I)$.[29]

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of **2**, **6–10**, **12–20**, **22**, **24**, **26–28**, **30**, **34**, **35**, **37–41**, **43–68**, and TMS enol ethers of **6** and **68**, Tables S1 and S2 listing ^{13}C NMR and ^1H NMR data for synthetic intermediates and model compounds **6–9**, **13**, **15–26**, **28–30**, **34**, **35**, **40–46**, **49–68**, and TMS enol ether of **6** (121 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(29) The authors have deposited atomic coordinates for structure **60** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.