# The Diene–Transmissive [4 + 2]-Cycloaddition Strategy: Stereoselective Synthesis of Advanced Intermediates to Quassinoids

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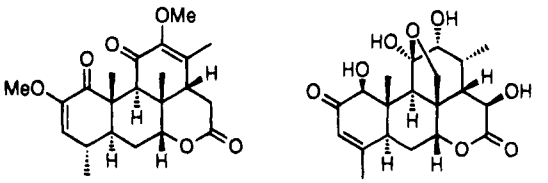
Complex intermediates to quassinoids, some optically active and containing many functional groups, were synthesized via a diene–transmissive Diels–Alder strategy. The stereochemistry of the key inter- and intramolecular cycloadditions was controlled by stereodefined groups on the preexisting C ring and on the tether.

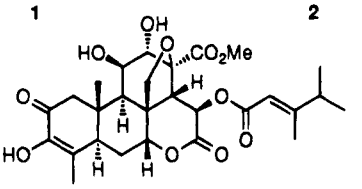
The quassinoids are highly oxygenated triterpenes isolated from plants of the genus *Simabouraceae*.[1] They have challenged the synthetic organic research community for over three decades and only recently have total syntheses appeared in significant numbers,[2,3] from Grieco's first synthesis of quassin (**1**) in 1980[4] to antileukemic glaucarubolone (**2**)[5] and bruceantin (**3**).[6] It is now acknowledged that their complex array of stereocenters and the extent of oxygenation of their carbon skeleton are at the center of their difficult reconstruction. Many members of this family of degraded steroids have a wide range of biological activities, including antineoplastic, antiviral, antimalarial, and insect antifeeding properties, and for that reason they have been the focus of intense research both from synthetic and biochemical laboratories.



**1**



**2**

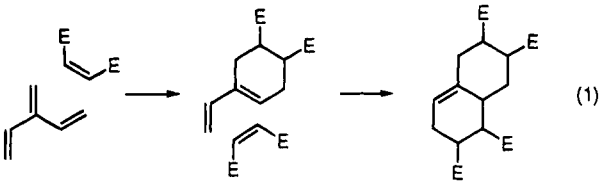


**3**

We recently communicated the preliminary study of a novel strategy to efficiently and stereoselectively construct the quassinoid framework via a diene–transmissive Diels–Alder reaction (eq 1).[7] We herein disclose the full account of this research including the preparation of an enantiomerically pure advanced tetracyclic intermediate with stereochemical control at eight chiral centers.

## Introduction

Although the diene–transmissive Diels–Alder reaction between the cross-conjugated triene 3-methylene-1,4-pentadiene and two dienophiles was described as early as 1955, this strategy has not been used to any significant extent in synthesis despite its apparent potential (eq 1).[8]



(1)

Tsuge and others investigated a series of intermolecular diene–transmissive [4 + 2]-cycloadditions on simple substituted cross-conjugated trienes (eq 2).[9,10] Several problems limited the application of the method. First, regioselectivity in the first cycloaddition occurred in some cases (e.g. **4a–c**) but not in others (e.g. **4d**). Second, preparing highly substituted trienes with control over the geometry of each double bond is not a task easily achieved and for that reason most of the trienes utilized were either monosubstituted or devoid of geometric isomerism. Lastly, there were inherent problems in using acyclic trienes in that many of them are unstable to the reaction conditions used for the Diels–Alder reaction (e.g. **4e,f**). For all these reasons, one of the double bonds in the cross-

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(1) For reviews, see: Polonsky, J. *Forts. Chem. Org. Naturst.* **1973**, *30*, 101; **1985**, *47*, 221.

(2) For a review of synthetic routes to quassinoids, see: Kawada, K.; Kim, W.; Watt, D. S. *Org. Prep. Proc. Int.* **1989**, *21*, 521.

(3) (a) Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764. (b) Stojanac, N.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853. (c) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Igarashi, M.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 1119. (d) Gross, R. S.; Grieco, P. A.; Collins, J. L. *J. Am. Chem. Soc.* **1990**, *112*, 9436. (e) Collins, J. L.; Grieco, P. A.; Gross, R. S. *J. Org. Chem.* **1990**, *55*, 5816. (f) Grieco, P. A.; Nargund, R. P.; Parker, D. T. *J. Am. Chem. Soc.* **1989**, *111*, 6287. (g) Kawada, K.; Kim, M.; Watt, D. S. *Tetrahedron Lett.* **1989**, *30*, 5989. (h) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 435.

(4) Grieco, P. A.; Ferriño, S.; Giovanni, V. *J. Am. Chem. Soc.* **1980**, *102*, 7586. Giovanni, V.; Ferriño, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539.

(5) Fleck, T. J.; Grieco, P. A. *Tetrahedron Lett.* **1992**, *33*, 1813. Grieco, P. A.; Collings, J. L; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078.

(6) Grieco, P. A.; VanderRoest, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 5841. Relay synthesis of bruceantin: Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528.

(7) Spino, C.; Liu, G. *J. Org. Chem.* **1993**, *58*, 817. Spino, C.; Tu, N. *Tetrahedron Lett.* **1994**, *35*, 3683.

(8) Blomquist, A. T.; Verdol, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 81. Bailey, J. W.; Economy, J. *J. Am. Chem. Soc.* **1955**, *77*, 1133. Bailey, W. J.; Cunov, C. H.; Nicholas, L. *J. Am. Chem. Soc.* **1955**, *77*, 2787.

(9) (a) Tsuge, O.; Wada, E.; Kanemasa, S.; Sakoh, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3221. (b) Tsuge, O.; Kanemasa, S.; Sakoh, H.; Wada, E. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3234. (c) Wada, E.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1198. (d) Motoki, S.; Matsuo, Y.; Terauchi, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 284.

(10) For examples with isodicyclopentadiene, see: Adam, W.; Deufel, T.; Finzel, R.; Griesbeck, A. G.; Hirt, J. *J. Org. Chem.* **1992**, *57*, 3991.

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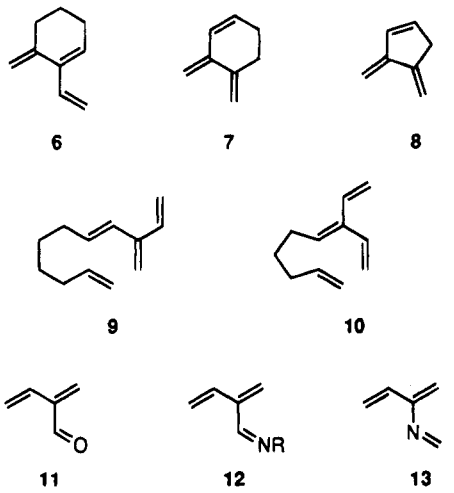
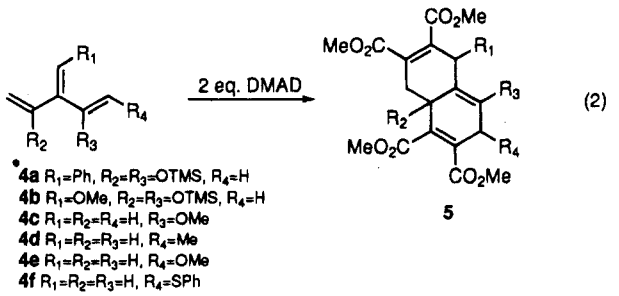



**Figure 1.** Methods to control regioselectivity in the diene–transmissive Diels–Alder strategy.

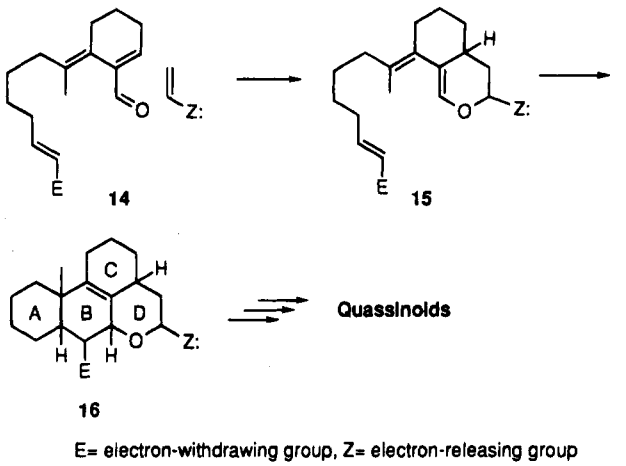
conjugated triene often had to be masked or generated at a later time.[11]



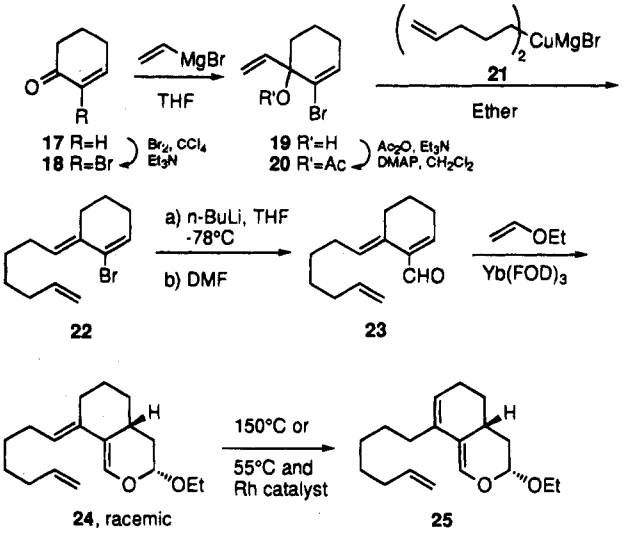

To render this strategy amenable to the synthesis of complex natural products, the above-mentioned problems, and several other issues, had to be resolved. The questions of stereo- and regioselectivity become particularly important as the number of asymmetric centers in the target molecule increases. Several options exist that circumvent the problem of regioselectivity and at the same time increase the potential of the strategy for the synthesis of complex polycyclic molecules. One of these involves cyclic trienes where one diene unit is constrained inside the cyclic structure. The top of Figure 1 displays a few examples (cf. **6**–**8**). In each structure one diene unit is fixed in the *transoid* configuration and thus cannot participate in a Diels–Alder reaction. After the first cycloaddition, the transmitted diene unit becomes fixed in the cisoid conformation and can participate in the second cycloaddition. Another option combines inter- and intramolecular cycloadditions. For example, in the acyclic triene **9**, the intramolecular cycloaddition would be expected to proceed first and with regioselectivity because of geometric constraints. The subsequent intermolecular reaction could then take place on the transmitted diene. A third option differentiates the two diene units by substituting a carbon for a heteroatom (cf. **11**–**13**). The heteroatom will usually confer electron deficiency to the diene and react preferentially with electron-rich dienophiles. Depending on the heteroatom and its position, it should be possible to effect good differentiation of the diene units.

(11) See examples in Tsuge, O.; Kanemasa, S.; Wada, E.; Sakoh, H. *Yuki Gosei Kagaky Kyohashi.* **1986**, *44*, 756 (Jpn) and references cited therein.

**Scheme 1**




**Scheme 2**

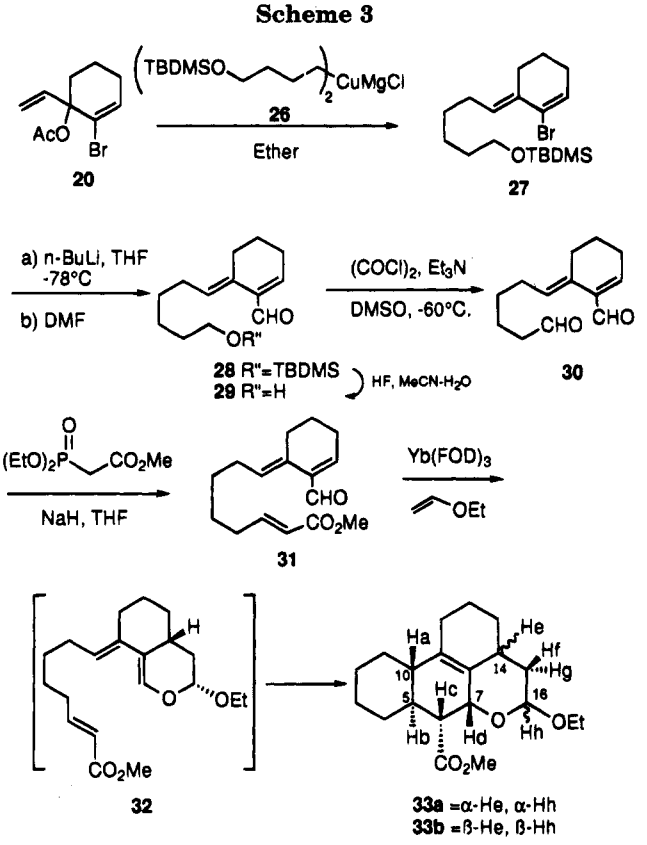



It can be imagined that the combination of two or more of these options leads to interesting synthetic possibilities. We envisaged that the tetracyclic framework of the quassinoids could be stereoselectively and efficiently prepared using a diene–transmissive Diels–Alder strategy where an initial intermolecular inverse-electron demand [4 + 2]-cycloaddition of a cyclic unsaturated aldehyde and an electron-rich dienophile would transmit a second diene unit, allowing an intramolecular Diels–Alder reaction to take place (Scheme 1). The most important features in controlling in this strategy was the stereochemical outcome of both Diels–Alder cycloadditions, and this account deals with these issues. We anticipated that an R group on ring C of the precursor **14** could perhaps direct the approach of the incoming dienophile in the initial hetero-Diels–Alder reaction. Preferably, the R group would either be part of natural quassinoids or, at least, be useful for further elaboration. The intramolecular Diels–Alder could be influenced by chiral centers both on rings C and D or on the tether.

The initial studies related to the feasibility of the approach. To that effect, we prepared the model compound **23** in five steps from 2-cyclohexen-1-one (**17**) as described in Scheme 2. A bromination–elimination reaction of **17** gave the vinylic bromide **18**[12] (77%) which

(12) Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro M. A. *J. Org. Chem.* **1982**, *47*, 1855.

**Scheme 3**




was reacted with vinylmagnesium bromide in THF to provide alcohol **19** in 73% yield. The acetate **20**, derived from **19** (79%), was regioselectively displaced, in a $S_N2'$ sense, by the cuprate reagent **21** to afford triene **22** as a single geometric isomer.[13] The lithium–halogen exchange reaction of **22** with *n*-butyllithium followed by trapping of the vinyl anion with DMF gave the aldehyde **23** in 80% yield for two steps. The ytterbium-catalyzed,[14] inverse-electron demand, Diels–Alder cycloaddition between **23** and ethyl vinyl ether (as solvent) at room temperature proceeded with complete *endo* selectivity to afford the racemic dihydropyran **24** in 88% yield. Unfortunately all attempts to cyclize the triene **24** failed due to competing double bond migration. The conjugated diene in **24** is electron-rich and fixed in a cisoid conformation and should be quite reactive with an electron-poor dienophile. We surmised that activating the dienophile with an electron-withdrawing group would allow the cycloaddition to proceed at room temperature, thus alleviating the alkene migration problem.

This hypothesis was validated by preparing the model compound **31** in eight steps from 2-cyclohexen-1-one (**17**) as described in Scheme 3. The acetate **20** was again regioselectively displaced in a $S_N2'$ sense, this time by the cuprate reagent **26**[15] to afford the diene **27** as a single geometric isomer. The lithium–halogen exchange reaction of **27** and trapping with DMF gave aldehyde **28** in 80% yield from the acetate. Removal of the silyl group with hydrofluoric acid proceeded in 92% yield to give **29** and was followed by an oxidation of the resulting primary alcohol using the Swern reaction conditions[16] to afford

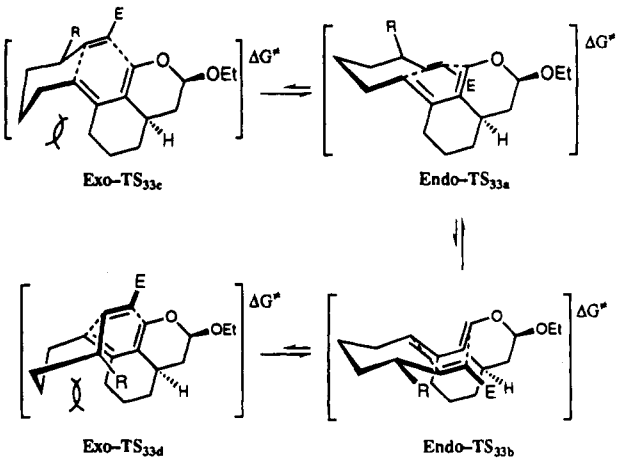



**Figure 2.** Chair-like transition states for the intramolecular cycloaddition of **32**.

the dialdehyde **30** in 85% yield. The latter underwent a chemoselective Wadsworth–Emmons reaction with methyl diethylphosphonoacetate (MDEPA) to give the desired *E*-α,β-unsaturated ester **31** in 87% yield.

The inverse-electron demand Diels–Alder cycloaddition between **31** and ethyl vinyl ether at room temperature was immediately followed by an *endo*-selective intramolecular Diels–Alder cycloaddition to give the tetracyclic compounds **33a** and **33b** in 87% yield in a 6:1 ratio (Scheme 3).[17] The racemic intermediate **32** could not be isolated. The stereochemistry of the major cycloadduct **33a** was deduced from NOE experiments (positive enhancements between $H_a$–$H_d$, $H_c$–$H_d$ (strong), $H_d$–$H_f$, $H_g$–$H_h$, and no enhancement between $H_b$ and $H_c$) and from the coupling constants of $H_c$ ($J_{Hb-c} = J_{Hc-d}$ = 9.3 Hz). Later, a single-crystal X-ray analysis confirmed this assignment.[18] The minor isomer **33b** could not be obtained in pure form, but the following coupling constants could be clearly discerned: $J_{Hb-c}$ = 12.5 Hz, $J_{Hc-d}$ = 6.5 Hz, $J_{Hf-h}$ = 2.5 Hz, $J_{Hg-h}$ = 9.8 Hz. These are in agreement with the proposed structure where $H_b$–$H_c$ must be *trans* and $H_c$–$H_d$ are *cis*. Thus, both isomers have the same stereochemistry at $C_5$, $C_6$, $C_7$, and $C_{10}$, arising from two *endo*-chair-like transition states $\mathbf{TS_{33a}}$ and $\mathbf{TS_{33b}}$ (R = H), which is consistent with our predictions based on the literature (Figure 2, R = H).[19] The

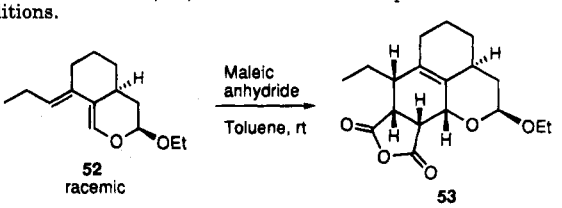
(13) Crabbé, P.; Dollat, J.-M.; Gallina, J.; Luche, J.-L.; Velarde, E. *J. Chem. Soc., Perkin Trans. 1* **1978**, 730.

(14) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721.

(15) The precursor to reagent **26** was prepared by protecting 4-chloro-1-butanol as its *tert*-butyldimethylsilyl ether (TBDMSOTf, $Et_3N$, $CH_2Cl_2$).

(16) Mancuso, A. J.; Juang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

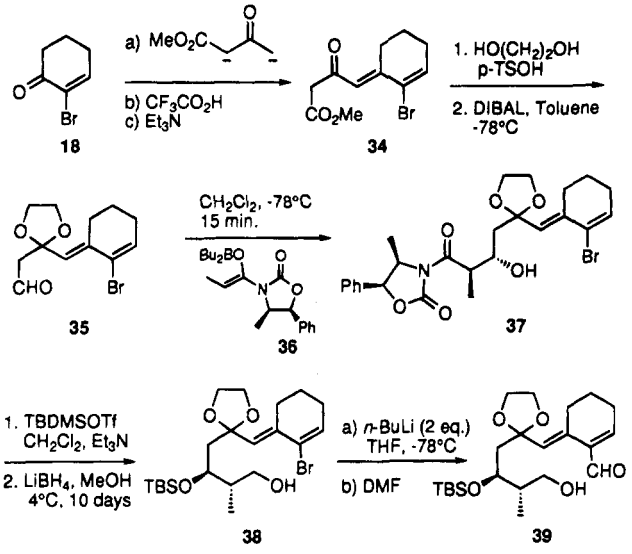
(17) This preference for α-attack by the dienophile was even more pronounced in the case of compound **52** reacting intermolecularly with maleic anhydride (24 h, rt in toluene). A single cycloadduct (**53**) was isolated in 92% yield. Its structure was secured by single-crystal X-ray crystallography. Caution should be exercised in comparing the [4 + 2]-cycloaddition of **33**, **41**, and **52** since all were performed in different conditions.




(18) The author has deposited atomic coordinates for structures **33a**, **42c**, and **53** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(19) See examples of internally substituted trienes in: Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187 and references cited therein.

**Scheme 4**

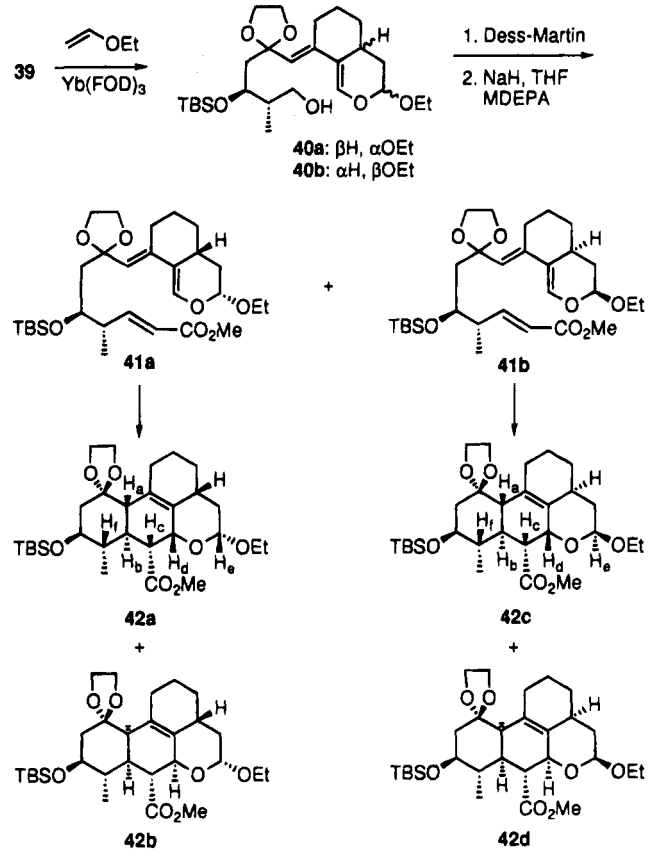



*exo* transition states are disfavored due to an unfavorable interaction between the methylene residue at $C_2$ and $C_{11}$ as shown.

We then attempted to reverse the directing effect of the $C_{14}$ and $C_{16}$ centers while controlling the absolute stereochemistry at $C_5$, $C_6$, $C_7$, and $C_{10}$. We were confident that it would be possible to achieve this task by placing one or more suitable chiral substituents that would adopt an equatorial position in the chair-like transition state of the IMDAC of **32** (Figure 2, R ≠ H).[19] To that effect we constructed the enantiomerically pure precursors **41** containing a (*tert*-butyldimethylsilyl)oxy and a methyl group at $C_3$ and $C_4$, respectively (cf. Scheme 5). This model study involved the two diastereomers **41a** and **41b** for pratical reasons and at the same time it would be interesting to observe the directing effect of the tether substituents on these two different $C_{14,16}$ isomers.

The synthesis started with the addition of the dianion of methyl acetoacetate[20] to 2-bromo-2-cyclohexen-1-one (**18**) to give, after elimination of water with neat trifluoroacetic acid, the dienone **34** (Scheme 4).[21] Protection of the ketone as the 1,3-dioxolane was followed by reduction of the methyl ester with DIBAL-H in toluene at −78 °C to yield 70% of the aldehyde **35** along with 25% of the primary alcohol resulting from overreduction. The latter could be separated and oxidized for a total yield of 90% of the desired aldehyde **35**. Compound **35** was then subjected to the Evans asymmetric aldol methodology to furnish the optically pure oxazolidinone derivative **37** (>99% by GC analysis).[22] Protection of the secondary alcohol was achieved using *tert*-butyldimethylsilyl triflate and triethylamine in dichloromethane (79%) and the oxazolidinone auxiliary was removed by careful reduction with lithium borohydride over a 10 day period, giving an 83% yield of the alcohol **38**. Other reducing agents such as $LiAlH_4$ and DIBAL-H gave unsatisfactory yields of the alcohol. The α-methyl substitution in **37** may sterically hinder attack at the desired amide carbonyl. Nonetheless, a metal–halogen exchange on the resulting unprotected primary alcohol using 2 equiv of *n*-butyllithium was successful and trapping with DMF afforded the aldehyde **39** in 80% yield. Oxidation of **39** to the corresponding dialdehyde could be achieved using PDC in dichloromethane. However, all attempts to subsequently react the saturated aldehyde chemoselectively failed probably due to steric hindrance provided by the α-methyl group.

**Scheme 5**




We therefore carried out the ytterbium-catalyzed hetero-Diels–Alder cycloaddition on the hydroxy aldehyde **39** and obtained a good yield of the diastereomeric cycloadducts **40a** and **40b** with complete *endo* selectivity as anticipated (Scheme 5). Not unexpectedly, the two inseperable diastereomers were formed in a 1:1 ratio. The primary alcohol was then oxidized to the aldehyde using the Dess–Martin periodinane[23] followed by a standard Wadsworth–Emmons reaction with the anion of methyl diethylphosphonoacetate (MDEPA) to give the *E*-α,β-unsaturated esters **41a** and **41b** in quantitative yield (Scheme 5). These two inseparable diastereomeric esters could be isolated but slowly underwent a stereoselective cycloaddition reaction at 39 °C to give 89% of essentially three separable tetracyclic compounds **42a–c**. $^1H$ NMR integration of the $C_6$ protons in the crude reaction mixture indicated a 1:1.7 ratio of **42a**:**42c**. The relative ratio of compound **42b** could not be ascertained in the crude mixture because of its broad signals (vide infra). However, the isolated ratio of **42a**:**42b** was 3:2, giving an overall ratio for **42a**:**42b**:**42c** of 1.5:1:2.4.[24] The proton NMR spectrum of **42c**, before recrystallization, displayed small peaks which may belong to a fourth tetracyclic compound (≤5%). The identity of the fourth isomer could

(20) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(21) Bérubé, G.; Fallis, A. G. *Can. J. Chem.* **1991**, *68*, 77.
(22) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23 and references therein.
(23) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
(24) Upon chromatography some quantity of the isomer **42c** was lost since its isolated ratio with **42a** was 1:1. However, the NMR spectra of the crude mixture gave unmistakably a true ratio of 1:1.7 (**42a**:**42c**) for these two compounds.

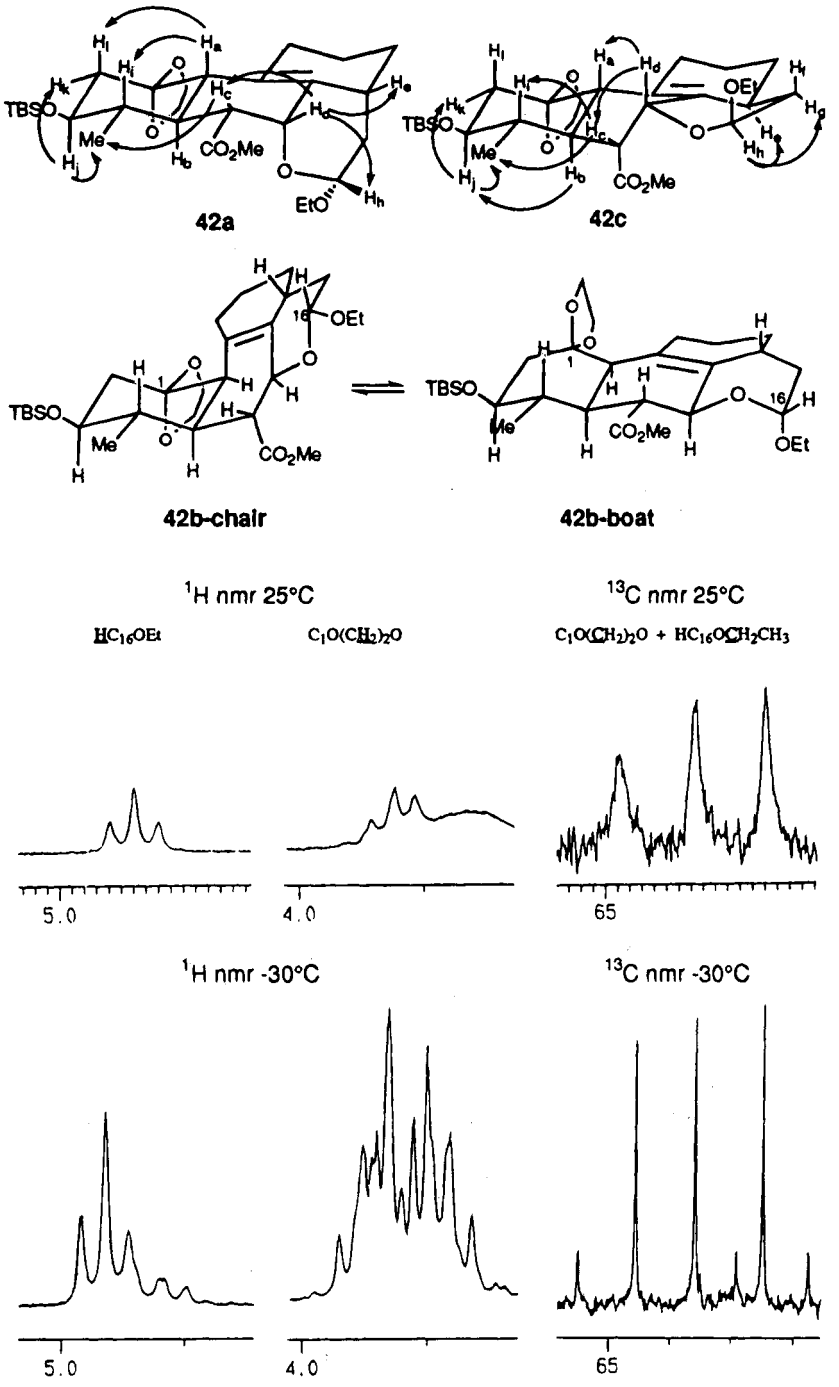



**Figure 3.** NOE effects in tetracycles **42a** and **43c** (top). Partial $^1$H and $^{13}$C NMR spectra of **42b** at 25 and −30 °C showing two equilibrating conformations (bottom).

not be ascertained but we believe it could be **42d** on the basis of some of its $^1$H NMR signals and from examination of the possible transition states (vide infra). The two major tetracycles **42a** and **42c** had the desired absolute stereochemistry at $C_5$, $C_6$, $C_7$, and $C_{10}$ as evidenced by 2D NOESY experiments (Figure 3, top). For **42a**, enhancements between $H_a$−$H_i$, $H_c$−$H_d$, $H_c$-Me, $H_d$−$H_e$, and $H_d$−$H_h$ were observed. Note that $H_a$ and $H_e$ have coincidental signals in the $^1$H NMR as demonstrated by COSY experiment. However, since these two protons are far apart in the molecule, they must interact with different protons in the NOESY spectrum, and hence, there is no confusion in interpreting the latter spectrum. The only difficulty was to determine whether there was an NOE enhancement between $H_d$−$H_e$ or $H_d$−$H_a$ or both. Analysis of the possible conformations of **42a** suggests that it should be $H_d$−$H_e$ but since $H_a$−$H_d$ and $H_e$−$H_h$ must be *syn* whereas $H_b$−$H_c$ must be *anti*, it is not necessary to know this particular result. For **42c**, enhancements between $H_a$−$H_d$, $H_b$−$H_j$, $H_c$−$H_d$, $H_c$−Me, $H_c$−$H_i$, and $H_e$−$H_h$ were evidence of the proposed structure (here also $H_a$−$H_d$ and $H_e$−$H_h$ must be *syn* whereas $H_b$−$H_c$ must be *anti*). Other enhancements for these two isomers are shown in Figure 3. Later, a single-crystal X-ray crystallographic analysis confirmed the structure of **42c**.[18] The proton and carbon NMR spectra of the minor isomer **42b** showed two distinct conformations at −30 °C (Figure 3, bottom). We believe two conformations, **42b**-chair and **42b**-boat, slowly equilibrate at 25 °C as shown by the broadening of NMR signals which become sharp again above 40 °C. This is indicative of a *cis* fusion between rings A and B (steroid lettering) as

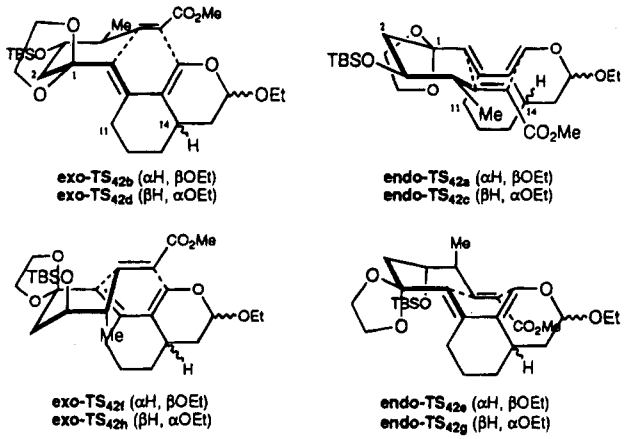


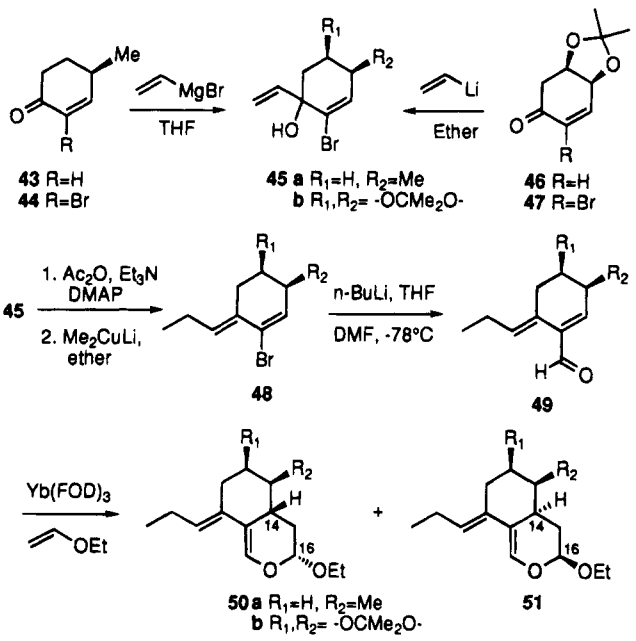

**Figure 4.** Possible transition states for the IMDAC of **41a** and **41b**.

proposed. The stereochemistry at $C_{14,16}$ in **42b** had to be the same as in **42a** since their added ratio is equal to that of **42c**. Comparison of the proton NMR of **42b** with that of other analogous tetracycles of known structures confirmed this affirmation.[7] Figure 3 shows the partial $^1H$ and $^{13}C$ NMR spectra of **42b** and the two conformations we think are in involved in this equilibrium. From integration of the proton NMR signals, the ratio of the two conformations is 4:1 at −30 °C. While it was not possible to determine which was predominating, molecular mechanics calculations favored conformation **42b**-chair by 2.6 kcal/mol. The minimized conformation of **42b**-boat showed a somewhat distorted boat conformation for the left-hand ring.

The major tetracyclic compounds **42a** and **42c** are thought to arise via the *endo* chair-like transition states **TS$_{42a}$** and **TS$_{42c}$**, respectively, where the methyl and (*tert*-butyldimethylsilyl)oxy groups are oriented in equatorial positions (Figure 4). These transition structures are preferred to the chair-like transitions states **TS$_{42e-h}$** where the same tether substituents are axial. In the analogous cycloaddition of intermediate **32** (cf. Scheme 2), the *exo*-**TS$_{33c}$** and *exo*-**TS$_{33d}$** were unable to compete with their *endo* counterpart because of steric repulsion between the methylene residues at $C_2$ and $C_{11}$ (cf. Figure 2).[7,17] However, in the case of the cycloaddition of **41a**, the 1,3-dioxolane moiety at $C_1$ may slightly raise the energy of the *endo* transition state **TS$_{42a}$** due to an unfavorable interaction with the methylene protons at $C_{11}$, thus allowing the *exo*-**TS$_{42b}$** to compete. This would explain the formation of appreciable amounts of the cycloadduct **42b**. The difference in energy between *endo*-**TS$_{42c}$** and *exo*-**TS$_{42d}$** must be larger than that between **TS$_{42a}$** and **TS$_{42b}$**, thus explaining the small amount of adduct **42d** obtained.

Although the stereoselectivity observed in the IMDAC of the model **41a** was modest (essentially 3:2), it constitutes a major reversal of selectivity since in the case of the unsubstituted tether model **32**, the undesired $C_{14}$ isomer was predominating by a ratio of 6:1.[25] Achieving control over the absolute stereochemistry at $C_{14}$ was the next necessary step. We investigated this control on the model aldehydes **49**, which were synthesized using a route analogous to the preparation of compounds **24** and **31** (Scheme 6). Racemic enone **43** was prepared from

**Scheme 6**




*p*-methylanisole.[26] Bromination–elimination of **43** gave vinylic bromide **44** in 64% yield. Addition of vinylmagnesium bromide to this compound produced **45a** as a mixture of two isomeric alcohols in 84% yield. Acetylation (70%) followed by $S_N2'$ displacement of the resulting allylic acetate with lithium dimethylcuprate afforded a 72% yield of the *E*-exocyclic olefin **48a**. The metal–halogen exchange reaction was then used, as before, to obtain the desired aldehyde **49a** in 72% yield. Optically pure enone **46** was prepared in four steps from (−)-quinic acid[27] and was submitted to a similar sequence of reactions as per **43** to afford the optically active aldehyde **49b** in a comparable overall yield. Note that the reaction of **47** with vinylmagnesium bromide gave predominantly the 1,4-addition product even in the presence of excess magnesium dibromide or anhydrous cerium trichloride.[28] Delivery of the reagent to the olefin by chelation to the isopropylidene oxygen is presumably the cause of this unexpected Michael addition. Reaction of **47** with vinyllithium in ether, on the other hand, gave a 53% yield of a single 1,2-addition product (**45b**) and traces of the 1,4-adduct.

The ytterbium-catalyzed cycloaddition of **49a** ($R_1$ = H, $R_2$ = Me) with ethyl vinyl ether gave a 3.5:1 mixture of inseparable stereoisomers **50a** and **51a** in 87% yield (GC analysis) (Scheme 6). Unfortunately, we could not rely on the NOESY spectrum of **50a** to assign its stereochemistry because of overlapping resonances. However, we compared the $^{13}C$ NMR resonances of the major and minor isomers and found them to be consistent with structures **50a** and **51a**, respectively (Figure 5).[29] Table 1 lists the relevant $^{13}C$ chemical shifts of both isomers

(25) The different conditions used in the cycloadditions of **33** and **41** may also concur in the reversal of stereochemistry.

(26) Kwart, H.; Conley, R. A. *J. Org. Chem.* **1973**, *38*, 2011. The hydrolysis of 1-methoxy-4-methylcyclohexadiene was carried out in refluxing 6 N aqueous sulfuric acid.

(27) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A; Danishefsky, S. J. *J. Org. Chem.* **1989**, 54, 3738.

(28) $CeCl_3$ has been shown to favor the 1,2-addition of Grignard reagents to unsaturated carbonyls, see: Imamoto, I.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(29) See: Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. In *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1989; pp C50–C65.

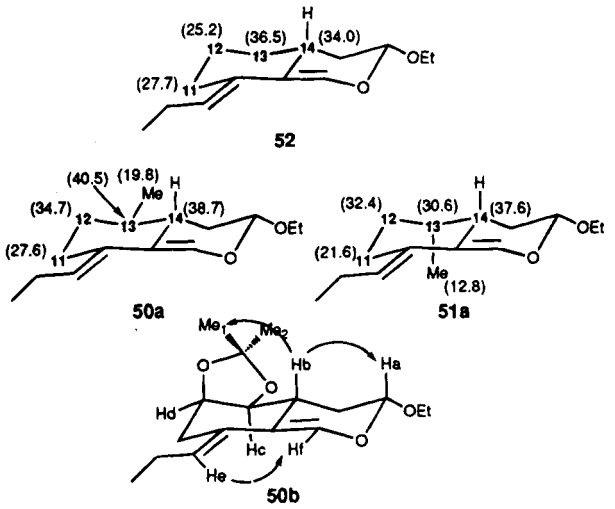



**Figure 5.** 3D structures of **50a**, **50b**, and **51a**. Numbers in parentheses refer to $^{13}C$ NMR resonances, numbered atoms refer to carbons in Table 1 (see text for discussion). Arrows indicate observed NOE effects in **50b**.

**Table 1. Chemical Shifts (ppm) of Relevant Carbons in the Parent Oxabicyclo 52 and the Calculated and Observed Shifts in the Corresponding Two Isomeric Methyl Compounds 50a and 51a**

| | | 50a | | 51a | |
|---|---|---|---|---|---|
| carbon | 52 | calcd | expt | calcd | expt |
| 11 | 27.7 | 27.7 | 27.6 | 22.3 | 21.6 |
| 12 | 25.2 | 34.1 | 34.7 | 30.3 | 32.4 |
| 13 | 36.5 | 42.1 | 40.5 | 37.6 | 30.6 |
| 14 | 34.0 | 42.9 | 38.7 | 39.2 | 37.6 |
| Me | | 20.3 | 19.8 | 12.0 | 12.8 |

with those predicted from the literature starting from the parent compound **52** which we prepared in an analogous way. Cycloaddition of **49b** ($R_1$,$R_2$ = -$OCMe_2O$-) with ethyl vinyl ether gave a 66% pure yield of the desired cycloadduct **50b** and 12% of an inseparable 1:1 mixture of two compounds.[30] The stereochemistry of the adduct **50b** was unambiguously established from its $^1H$ NMR and NOESY spectra. Enhancements between $H_a$–$H_b$, $H_b$–$Me_1$, $H_c$–$H_d$, and $H_e$–$H_f$ were proof of the proposed structure (Figure 5). As hoped, the methyl and acetonide substituents were able to direct the attack of the incoming ethyl vinyl ether to the opposite face of the molecule by steric hindrance. We believe that this stereoselectivity will increase when more elaborate dienophiles (substituted with oxygens at both carbons) are used. Cycloadduct **50b** is a particularly interesting model as it is optically active and contains useful functionalities for further elaboration of ring C in the quassinoids.

In conclusion we have demonstrated the power of the diene–transmissive Diels–Alder strategy for the synthesis of complex intermediates to quassinoids, some optically pure. These contain functional groups that can be used for further elaboration into natural quassinoids. More importantly we have shown that the stereochemistry of the intramolecular cycloaddition in our diene–transmissive strategy can be controlled by the introduction of stereodefined groups on the tether. Prior control of the $C_{14}$ stereocenter was also achieved. The questions of the $C_{10}$-methyl group and of the transformation of the endocyclic double bond in the tetracyclic intermediates remain and we are currently studying ways to answer them. The strategy will be used in the total synthesis of a natural quassinoid in the near future.

(30) No definite structures could be assigned to either minor isomers, though one of them could perhaps be **51b** on the basis of proton NMR.

## Experimental Section

All solvents were distilled from sodium–benzophenone with the exception of di- and tetrachloromethane and dimethyl sulfoxide which were distilled from calcium hydride. All reactions were performed under an atmosphere of argon unless otherwise stated. Flash column chromatography was done using Merck 60 silica gel. NMR spectra were taken in $CDCl_3$ at 250 or 360 MHz, and IR spectra were recorded in $CHCl_3$. Gas chromatography was performed on a DB-1 capillary column with FID detector.

**2-Bromo-1-vinyl-2-cyclohexen-1-ol (19).** 2-Bromo-2-cyclohexen-1-one (**18**) (4.35 g, 24.9 mmol) in diethyl ether (40 mL) was added slowly to a solution of vinylmagnesium bromide (50 mL, 1 M in THF) and diethyl ether (300 mL) at −78 °C. The mixture was stirred for 30 min at −78 °C and then quenched with saturated aqueous ammonium chloride (150 mL). The aqueous phase was extracted with diethyl ether (2 × 100 mL). The organic layers were combined and washed with saturated aqueous sodium chloride (100 mL) and dried over magnesium sulfate. The solvents were removed under reduced pressure. The product was then purified by flash column chromatography eluting with hexanes–ethyl acetate (5:1) to yield pure alcohol **19** as a colorless oil (3.69 g, 73%). $^1H$ NMR ($CDCl_3$): δ 6.14 (t, 1H, $J$ = 4.1 Hz), 5.75 (dd, 1H, $J$ = 17.2, 10.6 Hz), 5.22 (dd, 1H, $J$ = 17.2, 1.2 Hz), 5.11 (dd, 1H, $J$ = 10.6, 1.2 Hz), 2.61 (s, 1H), 2.05–1.52 (m, 6H). $^{13}C$ NMR: 141.8 (d), 132.5 (d), 128.1 (s), 114.5 (t), 74.1 (s), 37.0 (t), 27.6 (t), 18.5 (t). IR ($CHCl_3$, $cm^{-1}$): 3560 (ms), 3540–3360 (bw), 1635 (ms). MS ($m/z$, intensity): 204 ($M^+$, 5), 202 ($M^+$, 5), 177 (60), 175 (50), 123 (100), 95 (80). Exact mass calcd for $C_8H_{11}{}^{81}BrO$ 203.9961, found 203.9961; calcd for $C_8H_{11}{}^{79}BrO$ 201.9993, found 201.9986. Anal. Calcd for $C_8H_{11}BrO$: C, 47.32; H, 5.46; Br, 39.35. Found: C, 47.43; H, 5.41; Br, 39.17.

**6-Acetoxy-1-bromo-6-vinyl-1-cyclohexene (20).** Acetic anhydride (1.55 g, 15.2 mmol) was added to a mixture of compound **19**, DMAP (0.19 g, 1.6 mmol), and triethylamine (1.90 g, 19 mmol) at rt. Dichloromethane (2.8 mL) was added to the mixture to dissolve DMAP. The reaction mixture was stirred for 21 h at rt and it was then diluted with diethyl ether (10 mL). The solution was washed with 1 N hydrochloric acid (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The aqueous layers were separately extracted with diethyl ether (2 × 10 mL). The combined organic phases were washed with saturated aqueous sodium chloride (10 mL) and dried over anhydrous magnesium sulfate. Solvent evaporation under reduced pressure followed by flash chromatography eluting with hexanes–ethyl acetate (9:1) produced 1.45 g of **20** as a slightly pink oil (78%). $^1H$ NMR ($CDCl_3$): δ 6.30 (dd, 1H, $J$ = 5.3, 2.9 Hz), 5.90 (dd, 1H, $J$ = 17.4, 10.7 Hz), 5.29 (d, 1H, $J$ = 17.4 Hz), 5.28 (d, 1H, $J$ = 10.7 Hz), 2.62 (dt, 1H, $J$ = 12.6, 4.3 Hz), 2.30–1.98 (m, 3H), 2.07 (s, 3H), 1.81–1.62 (m, 2H). $^{13}C$ NMR ($CDCl_3$): δ 168.9 (s), 137.4 (d), 133.7 (d), 122.9 (s), 115.9 (t), 82.6 (s), 32.2 (t), 27.1 (t), 21.9 (q), 19.1 (t). IR ($CHCl_3$, $cm^{-1}$): 1735 (s), 1640 (ms).

***(E)*-2-Bromo-1-(6-hepten-1-ylidene)-2-cyclohexene (22).** A solution of 5-bromo-1-pentene (2 g, 13.4 mmol) in diethyl ether (8.4 mL) was charged in a dropping funnel, and 1 mL of this solution was added to a flask containing freshly activated magnesium turnings (0.35 g, 14.4 mmol) and diethyl ether (5 mL) at rt. When the reaction started, the remaining solution of the bromide was added dropwise to the flask. After the addition was finished, the temperature was raised and the reaction mixture was refluxed for 6 h.

The resulting cloudy solution of 4-pentenylmagnesium bromide (10 mL, 10 mmol) was added, via canula, to a suspension of dry copper iodide (0.95 g, 5 mmol) in diethyl ether (30 mL) at 0 °C. The mixture was stirred for 10 min, and then acetate **20** (0.66 g, 2.5 mmol) in diethyl ether (30 mL) was added. A yellow precipitate appeared immediately. The reaction mixture was stirred for 1 h at 0 °C and quenched

with saturated aqueous ammonium chloride (60 mL). The aqueous phase was separated and extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo followed by flash column chromatography eluting with hexanes yielded compound **22** as a colorless oil (0.55 g, 81%). $^1$H NMR ($CHCl_3$): $\delta$ 6.19 (t, 1H, $J$ = 4.5 Hz), 5.89–5.63 (m, 2H), 5.04–4.89 (m, 2H), 2.42 (dt, 2H, $J$ = 6.2, 1.5 Hz), 2.22–2.00 (m, 6H), 1.70 (qi, 2H, $J$ = 6.2), 1.40 (qi, 4H, $J$ = 3.6 Hz). IR ($CHCl_3$, cm$^{-1}$): 1640 (ms), 1595 (w). MS ($m/z$, rel intensity): 256 ($M^+$, $^{81}$Br, 100), 254 ($M^+$, $^{79}$Br, 100), 215 (60), 213 (45), 187 (72). Exact mass calcd for $C_{13}H_{19}{}^{81}Br$ 256.0651, found 256.0648; calcd for $C_{13}H_{19}{}^{79}Br$ 254.0671, found 254.0680.

**(*E*)-1-Formyl-6-(6-hepten-1-ylidene)-1-cyclohexene (23).** Bromide **22** (0.52 g, 2.0 mmol) in THF (25 mL) was added dropwise to a solution of *n*-BuLi (2.5 M in hexane, 1.3 mL, 3.1 mmol) in THF (1 mL) at −78 °C. The reaction mixture was stirred for 30 min, and then DMF (0.60 g, 8.2 mmol) was added slowly. The mixture was stirred for 5 h at −78 °C and then quenched with saturated aqueous ammonium chloride. The aqueous layer was separated and extracted with diethyl ether (3 × 15 mL). The combined organic portions were washed with brine (20 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography eluting with hexanes–ethyl acetate (15:1) to give **23** as a colorless oil (0.30 g, 67%). $^1$H NMR ($CHCl_3$): $\delta$ 9.46 (s, 1H), 6.55 (dt, 1H, $J$ = 7.0, 1.4 Hz), 6.50 (t, 1H, $J$ = 6.3 Hz), 5.76 (ddt, 1H, $J$ = 17.1, 10.3, 6.7 Hz), 4.95 (dq, 1H, $J$ = 17.1, 1.7 Hz), 4.89 (dq, 1H, $J$ = 10.2, 1.7 Hz), 2.40 (q, 2H, $J$ = 6.3 Hz), 2.30 (dt, 2H, $J$ = 6.3, 1.4 Hz), 2.10 (q, 2H, $J$ = 7.0 Hz), 2.02 (qm, 2H, $J$ = 6.7 Hz), 1.69 (qi, 2H, $J$ = 6.3 Hz), 1.45–1.34 (m, 4H). $^{13}$C NMR ($CDCl_3$): $\delta$ 194.0 (d), 161.8 (d), 138.9 (d), 138.2 (s), 129.9 (d), 128.6 (s), 114.2 (t), 33.6 (t), 28.8 (t), 28.6 (t), 27.6 (t), 27.1 (t), 25.1 (t), 21.8 (t). IR ($CHCl_3$, cm$^{-1}$): 1730 (w), 1690 (s). MS ($m/z$, rel intensity): 204 ($M^+$, 23), 203 (100), 163 (62). Exact mass calcd for $C_{14}H_{20}O$ 204.1515, found 204.1520.

**(±)-(*E*)-4-Ethoxy-10-(6-hepten-1-ylidene)-3-oxabicyclo-[4.4.0]dodec-1-ene (24).** The aldehyde **23** (0.22 g, 1.1 mmol) and tris(6,6,7;7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (0.18 g, 0.17 mmol) were dissolved in ethyl vinyl ether (2 mL). The solution was stirred for 4 days at rt. The excess ethyl vinyl ether was removed *in vacuo*, and the residue was purified by flash column chromatography eluting with hexanes–ethyl acetate (15:1) to yield the racemic triene **24** as a colorless oil (0.27 g 91%). $^1$H NMR ($CHCl_3$): $\delta$ 6.31 (d, 1H, $J$ = 1.9 Hz), 5.78 (ddt, 1H, $J$ = 17.0, 10.3, 6.7 Hz), 5.23 (dt, 1H, 7.3, 2.3 Hz), 4.97 (dq, 1H, $J$ = 17.0, 1.7 Hz), 4.91 (dm, 1H, $J$ = 10.3 Hz), 4.78 (dd, 1H, $J$ = 9.7, 1.8 Hz), 3.92 (dq, 1H, $J$ = 9.5, 7.1 Hz), 3.54 (dq, 1H, $J$ = 9.5, 7.1 Hz), 2.56 (dm, 1H, $J$ = 13.9 Hz), 2.30–2.20 (m, 1H), 2.10–1.96 (m, 4H), 1.94–1.87 (m, 2H), 1.84–1.76 (m, 1H), 1.72–1.63 (bt, 1H, $J$ = 13.6 Hz), 1.52–1.43 (m, 1H), 1.40–1.21 (m, 5H), 1.22 (t, 3H, $J$ = 7.1 Hz), 1.10 (ddd, 1H, $J$ = 14.5, 12.4, 3.0 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 139.0 (d), 135.3 (s), 134.9 (d), 121.7 (d), 119.8 (s), 114.2 (t), 99.6 (d), 64.3 (t), 36.5 (t), 34.1 (d), 33.7 (t), 33.3 (t), 29.4 (t), 28.5 (t), 27.8 (t), 27.3 (t), 25.23 (t), 15.2 (q). IR ($CHCl_3$, cm$^{-1}$): 1635 (s), 1625 (s). MS ($m/z$, rel intensity): 276 ($M^+$, 37), 230 (36), 186 (41), 161 (80), 147 (54), 135 (100). Exact mass calcd for $C_{18}H_{28}O_2$ 276.2090, found 276.2102. Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.11; H, 9.98.

**2-Bromo-3-{4-[(*tert*-butyldimethylsilyl)oxy]-1-hexylidene}-1-cyclohexene (27).** To a mixture of 4-chloro-1-[(*tert*-butyldimethylsilyl)oxy]butane (3.38 g, 15.2 mmol), magnesium turnings (0.41 g, 16.7 mmol), and diethyl ether (15 mL) were added iodoethane (0.05 mL) and a small crystal of iodine. The mixture was refluxed for 26 h under argon. The resulting cloudy solution of [4-[(*tert*-butyldimethylsilyl)oxy]-1-butyl]magnesium chloride was added to a suspension of dry copper iodide (1.45 g, 7.6 mmol) in diethyl ether (25 mL) at 0 °C. After the addition, the color changed to dark blue. To this solution was added acetate **20** (0.93 g, 3.8 mmol) in diethyl ether (25 mL). The reaction mixture was stirred for 1 h at 0 °C and then quenched with saturated aqueous ammonium chloride (100 mL). The aqueous phase was separated and extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride (100 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent in vacuo followed by flash column chromatography eluting with hexanes–ethyl acetate (50:1) gave 2.5 g (>100%) of compound **27** containing 1-[(*tert*-butyldimethylsilyl)oxy]-butane as an impurity. The product was used directly in next reaction. $^1$H NMR ($CDCl_3$): $\delta$ 6.18 (t, 1H, $J$ = 4.4 Hz), 5.85 (t, 1H, $J$ = 7.6 Hz), 3.58 (t, 2H, $J$ = 6.5 Hz), 2.41 (bt, 2H, $J$ = 6.2 Hz), 2.22–2.06 (m, 4H), 1.70 (qi, 2H, $J$ = 6.2 Hz), 1.62–1.12 (m, 6H), 0.87 (s, 9H), 0.02 (s, 6H). $^{13}$C NMR ($CDCl_3$): $\delta$ 132.3 (s) 131.1 (d), 131.1 (d), 124.4 (s), 63.2 (t), 32.7 (t), 29.2 (t), 27.7 (t), 26.9 (t), 26.0 (q), 25.8 (t), 25.6 (t), 22.2 (t), 18.4 (s), −5.3 (q). IR ($CHCl_3$, cm$^{-1}$): 3005 (w), 1600 (w). MS ($m/z$, rel intensity): 374 ($M^+$, $^{81}$Br), 372 ($M^+$, $^{79}$Br), 359 (3), 357 (3), 318 (80), 316 (80), 235 (100), 233 (100). Exact mass calcd for $C_{18}H_{33}BrOSi$ 372.1484, found 372.1509.

**2-Formyl-3-{4-[(*tert*-butyldimethylsilyl)oxy]-1-hexylidene}-1-cyclohexene (28).** A solution of 2.5 M *n*-BuLi in hexanes (4.2 mL, 9.2 mmol) was added dropwise to bromide **27** (2.3 g, 6.2 mmol) in THF (130 mL) at −78 °C. The reaction mixture was stirred for 30 min, and then DMF (1.8 g, 24.8 mmol) was slowly added. The mixture was stirred for an extra 5 h at −78 °C and then quenched with saturated aqueous ammonium chloride (50 mL). The aqueous layer was separated and extracted with diethyl ether (2 × 40 mL). The combined organic portions were washed with saturated aqueous sodium chloride (50 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by flash column chromatography eluting with hexanes–ethyl acetate (15:1) to give **28** as a colorless oil, 0.98 g (80% from acetate **20**). $^1$H NMR ($CDCl_3$): $\delta$ 9.46 (s, 1H), 6.63–6.57 (m, 2H), 3.56 (t, 2H, $J$ = 6.4 Hz), 2.39 (q, 2H, $J$ = 6.2 Hz), 2.31 (t, 2H, $J$ = 6.2 Hz), 2.11 (q, 2H, $J$ = 7.1 Hz), 1.69 (m, 2H), 1.54–1.42 (m, 2H), 1.39–1.21 (m, 4H), 0.85 (s, 9H), 0.01 (s, 6H). $^{13}$C NMR ($CDCl_3$): $\delta$ 193.8 (d), 151.4 (d), 138.2 (s), 129.9 (d), 128.5 (s), 63.0 (t), 32.6 (t), 29.1 (t), 27.8 (t), 57.1 (t), 25.9 (q), 25.5 (t), 25.1 (t), 21.8 (t), 18.2 (s), −5.4 (q). IR ($CHCl_3$, cm$^{-1}$): 2735 (w), 1734 (w), 1695 (s). MS ($m/z$, rel intensity): 322 (6, $M^+$), 304 (6), 265 (100), 247 (36). Exact mass calcd for $C_{19}H_{34}O_2Si$ 322.2344, found 322.2342.

**2-Formyl-3-{1-oxo-4-hexylidene}-1-cyclohexene (30).** Diene aldehyde **28** (0.58 g, 1.8 mmol) was dissolved in a 16 mL solution of a 60:1 mixture of acetonitrile and 48% aqueous hydrofluoric acid. The resulting solution was stirred for 1.5 h at rt, and then saturated aqueous sodium bicarbonate (10 mL) was added. The aqueous layer was separated and extracted with diethyl ether (2 × 10 mL). The combined organic portions were washed with saturated aqueous sodium chloride (15 mL). Evaporation of solvent *in vacuo* followed by flash column chromatography eluting with hexanes–ethyl acetate (1:1) yielded alcohol **29** as a colorless oil 0.35g (92%). $^1$H NMR ($CDCl_3$): $\delta$ 9.44 (s, 1H), 6.60–6.55 (m, 2H), 3.58 (t, 2H, $J$ = 6.1 Hz), 2.38 (q, 2H, $J$ = 6.1 Hz), 2.29 (bt, 2H, $J$ = 6.1 Hz), 2.10 (q, 2H, $J$ = 7.0 Hz), 1.83 (bs, 1H), 1.68 (qi, 2H, $J$ = 6.1 Hz), 1.58–1.47 (m, 2H), 1.43–1.31 (m, 4H). $^{13}$C NMR: $\delta$ 194.1 (d), 151.9 (d), 138.1 (s), 129.7 (d), 128.6 (s), 62.6 (t), 32.5 (t), 29.0 (t), 27.7 (t), 27.0 (t), 25.4 (t), 25.1 (t), 21.7 (t). IR ($CHCl_3$, cm$^{-1}$): 3625 (w), 3660–3350 (b). MS ($m/z$, rel intensity): 208 (56, $M^+$), 190 (66), 145 (50), 135 (73), 132 (65), 119 (100), 91 (90), 79 (89). Exact mass calcd for $C_{13}H_{20}O_2$ 208.1464, found 208.1468. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.02; H, 9.54.

A solution of dimethyl sulfoxide (222 mg, 2.84 mmol) in dichloromethane (2.8 mL) was added dropwise to a solution of oxalyl chloride (180 mg, 1.42 mmol) in dichloromethane (2.8 mL) at −60 °C. The reaction mixture was stirred for 5 min, and alcohol **29** (148 mg, 0.71 mmol) in dichloromethane (2 mL) was added at −60 °C. The reaction was stirred for 15 min, and then triethylamine (350 mg, 3.6 mmol) was added. After an additional 15 min of stirring, the cooling bath was removed and the reaction allowed to warm to rt. The reaction was quenched with water (10 mL) and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined

organic phases were washed with saturated aqueous sodium chloride (10 mL) and dried over magnesium sulfate. After removal of solvent *in vacuo*, the product was purified by flash column chromatography eluting with hexanes–ethyl acetate (3:1) to give **30** as a colorless oil (124 mg, 85%). $^1$H NMR ($CDCl_3$): $\delta$ 9.66 (t, 1H, $J$ = 1.8 Hz), 9.38 (s, 1H), 6.57–6.50 (m, 2H), 2.38–2.31 (m, 4H), 2.24 (bt, 2H, $J$ = 6.1 Hz), 2.07 (q, 2H, $J$ = 7.3 Hz), 1.68–1.49 (m, 4H), 1.42–1.30 (m, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 202.4 (d), 193.8 (d), 152.0 (d), 138.0 (s), 128.9 (d), 128.9 (s), 43.5 (t), 28.7 (t), 27.3 (t), 27.0 (t), 25.0 (t), 21.6 (t), 21.6 (t). IR ($CHCl_3$, cm$^{-1}$): 2730 (ms), 1725 (s). MS (*m/z*, rel intensity): 206 (39, M$^+$), 135 (36), 132 (100). Exact mass calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1313. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.62; H, 8.88.

**2-Formyl-3-{(*E*)-1-carbomethoxy-1-octen-4-ylidene}-1-cyclohexene (31).** Methyl diethylphosphonoacetate (89 mg, 0.41 mmol) was added slowly to a suspension of sodium hydride (60% in oil, 17 mg, 0.43 mmol) in dry THF (5 mL) at 0 °C. The reaction mixture was stirred for 1 h and then added to a solution of dialdehyde **30** (80 mg, 0.39 mmol) in THF (2 mL) via a canula. After 2 h of stirring at 0 °C, the reaction was quenched with water (1 mL). Then, the mixture was washed with 1 N aqueous hydrochloric acid (1.5 mL) and saturated aqueous sodium bicarbonate (5 mL). The aqueous layers extracted with diethyl ether. The combined organic portions were washed with saturated aqueous sodium chloride (5 mL) and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure followed by flash column chromatography eluting with hexanes–ethyl acetate (3:1) yielded product **31** (89 mg, 87%) as a colorless oil. $^1$H NMR ($CDCl_3$): $\delta$ 9.43 (s, 1H), 6.90 (dt, 1H, $J$ = 15.7, 7.0 Hz), 6.59–6.54 (m, 2H), 5.75 (dt, 1H, $J$ = 15.7, 1.4 Hz), 3.66 (s, 3H), 2.38 (q, 2H, $J$ = 6.0 Hz), 2.27 (bt, 2H, $J$ = 6.1 Hz), 2.18–2.04 (m, 4H), 1.67 (qi, 2H, $J$ = 6.1 Hz), 1.45–1.38 (m, 4H). $^{13}$C NMR: $\delta$ 194.0 (d), 167.0 (s), 152.0 (d), 149.4 (d), 138.2 (s), 129.4 (d), 128.9 (s), 120.9 (d), 51.3 (q), 32.0 (t), 28.8 (t), 27.7 (t), 27.5 (t), 27.1 (t), 25.2 (t), 21.8 (t). IR ($CHCl_3$, cm$^{-1}$): 2735 (w), 1725 (s), 1695 (s). MS (*m/z*, rel intensity): 262 (2, M$^+$), 195 (11), 137 (35), 110 (100). Exact mass calcd for $C_{16}H_{22}O_3$ 262.1570, found 262.1573. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.24; H, 8.46. Found: C, 73.18; H, 8.49.

**(±)-$\Delta^{9,17}$-(1*R*,3*R*,5*S*,10*S*,15*S*,16*R*)- and (±)-$\Delta^{9,17}$-(1*R*,3*S*,5*R*,-10*S*,15*S*,16*R*)-3-Ethoxy-16-carbomethoxy-2-oxatetracyclo-[7.7.1.0$^{5,17}$.0$^{10,15}$]heptadec-9-ene (33a and 33b).** The triene aldehyde **31** (35 mg, 0.13 mmol) and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (21 mg, 0.02 mmol) were dissolved in ethyl vinyl ether (2 mL). The solution was stirred for 5 days at rt. The excess ethyl vinyl ether was removed under reduced pressure, and the residue was purified by flash column chromatography eluting with hexanes–ethyl acetate (9:1) to yield a 6:1 mixture of isomers **33a** and **33b** (39 mg, 87%) as a white solid. **Isomer 33a.** $^1$H NMR ($CDCl_3$): $\delta$ 4.89 (t, 1H, $J$ = 7.2 Hz), 4.34 (dm, 1H, $J$ = 9.3 Hz), 3.72 (dq, 1H, $J$ = 10.0, 7.1 Hz), 3.64 (s, 3H), 3.40 (dq, 1H, $J$ = 10.0, 7.1 Hz), 2.68 (t, 1H, $J$ = 9.3 Hz), 2.19–2.17 (m, 2H), 2.14–2.12 (m, 1H), 1.99 (ddd, 1H, $J$ = 13.6, 6.7, 4.3 Hz), 1.96–1.87 (m, 2H), 1.83–1.76 (m, 2H), 1.76–1.62 (m, 3H), 1.61–1.51 (m, 1H), 1.43–1.34 (m, 1H), 1.28–1.13 (m, 4H), 1.16 (t, 3H, $J$ = 7.1 Hz), 1.11–0.96 (m, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 174.0 (s), 131.9 (s), 131.1 (s), 98.2 (d), 63.3 (d), 62.5 (t), 51.3 (q), 51.1 (d), 40.4 (d), 40.2 (d), 35.5 (t), 33.3 (t), 30.4 (d), 29.4 (t), 29.1 (t), 26.3 (t), 26.1 (t), 24.8 (t), 22.6 (t), 15.2 (q). IR ($CHCl_3$, cm$^{-1}$): 1735 (s), 1620 (w), 1595 (w). MS (*m/z*, rel intensity): 334 (13, M$^+$), 288 (70), 185 (52), 91 (100). Exact mass calcd for $C_{20}H_{30}O_4$ 334.2145, found 334.2139. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.81; H, 9.04. Found: C, 71.80; H, 8.82. **Isomer 33b.** $^1$H NMR ($CDCl_3$): $\delta$ 4.51 (dd, 1H, $J$ = 9.8, 2.5 Hz), 3.84 (dm, 1H, $J$ = 6.5 Hz), 3.79 (dq, 1H, $J$ = 10.0, 7.1 Hz), 3.66 (s, 3H), 3.40 (dq, 1H, $J$ = 10.0, 7.1 Hz), 2.52 (dd, 1H, $J$ = 12.5, 6.5 Hz), 2.19–0.9 (m, 19H), 1.15 (t, 3H, $J$ = 7.1 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 172.1 (s), 134.6 (s), 127.5 (s), 101.6 (d), 70.6 (d), 63.9 (t), 50.5 (q), 44.4 (d), 41.1 (t), 36.6 (d), 34.8 (d), 30.7 (t), 30.4 (d), 29.1 (t), 28.9 (t), 27.0 (t), 26.8 (t), 25.9 (t), 21.9 (t), 15.1 (q).

**(*E*)-2-Bromo-1-{3-carbomethoxy-2-oxo-1-propylidene}-2-cyclohexene (34).** Methyl acetoacetate (0.67 g, 5.7 mmol) was added dropwise to a suspension of NaH (0.16 g, 6.7 mmol) in dry THF (10 mL) at 0 °C. After the effervescence had stopped, the reaction mixture was allowed to stir at that temperature for an additional 15 min followed by the dropwise addition of *n*-BuLi in hexane (2.2 M, 2.6 mL, 5.7 mmol). Stirring was continued for an additional 1 h before the dropwise addition of 2-bromo-2-cyclohexen-1-one (**18**) (1 g, 5.7 mmol) in dry THF (3 mL). The mixture was stirred at 0 °C for 1 h before being quenched with a saturated solution of ammonium chloride (3 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 5 mL) The combined organic layers were washed with brine (15 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (1:1) gave 2-bromo-1-{3-carbomethoxy-2-oxo-1-propyl}-1-hydroxy-2-cyclohexene as a colorless oil (1.43 g, 85%). The $\beta$-keto ester product existed as an equilibrium between the keto and enol forms. **Keto Form.** $^1$H NMR ($CDCl_3$): $\delta$ 6.21 (t, 1H, $J$ = 3.7 Hz), 3.72 (s, 3H), 3.53 (s, 2H), 3.35 (bs, 1H), 3.16 (d, 1H, $J$ = 16.4 Hz), 2.81 (d, 1H, $J$ = 16.4 Hz), 2.14–1.97 (m, 4H), 1.82–1.71 (m, 1H), 1.67–1.58 (m, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 202.9 (s), 167.3 (s), 133.9 (d), 128.2 (s), 72.4 (s), 52.4 (q), 51.5 (t), 50.5 (t), 36.2 (t), 27.8(t), 18.5 (t). **Enol Form.** $^1$H NMR ($CDCl_3$): $\delta$ 12.18 (s, 1H), 6.20 (t, 1H, $J$ = 3.7 Hz), 5.09 (s, 1H), 3.72 (s, 3H), 2.82 (d, 1H, $J$ = 14.5 Hz), 2.41 (d, 1H, $J$ = 14.5 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 174.0 (s), 172.7 (s), 133.5 (d), 129.1 (s), 92.4 (d), 72.5 (s), 51.3 (q), 45.5 (t), 35.7 (t), 27.9 (t), 18.8 (t). IR ($CHCl_3$, cm$^{-1}$): 3600–3320 (br), 1748 (s), 1714 (s), 1646 (w). MS (*m/z*, rel intensity): 274 (M$^+$, 50), 272 (45), 262 (43), 261 (45), 259 (43), 232 (100), 230 (100). Exact mass calcd for $C_{11}H_{13}O_3{}^{79}Br$ 272.0048, found 272.0073; calcd for $C_{11}H_{13}O_3{}^{81}Br$ 274.0028, found 274.0041. Anal. Calcd for $C_{11}H_{15}O_4Br$: C, 45.38; H, 5.19; Br, 27.45. Found: C, 45.28; H, 5.22; Br, 27.43.

To a 200 mL round-bottomed flask charged with the above $\beta$-keto ester (1 g, 0.0034 mol) at 0 °C was added trifluoroacetic acid (5 mL, 0.06 mol). The mixture was allowed to stir at that temperature for 1 h before being quenched with a mixture of water (50 mL) and ether (50 mL). The organic layer was separated, washed with water (3 × 30 mL), neutralized with sodium bicarbonate, and stirred with triethylamine (5 mL) at room temperature for 30 min. It was then washed with brine (20 mL) and water (2 × 20 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (3:1) gave compound **34** as a colorless oil (0.65 g, 69%). **Keto Form.** $^1$H NMR ($CDCl_3$): $\delta$ 6.72 (t, 1H, $J$ = 4.7 Hz), 6.51 (s, 1H), 3.67 (s, 3H), 3.50, (s, 2H), 3.00–2.96 (m, 2H), 2.24 (dt, 2H, $J$ = 6.3, 4.7 Hz), 1.67 (qi, 2H, $J$ = 6.3 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 192.3 (s), 167.7 (s), 150.6 (s), 143.3 (d), 123.2 (d) 122.3 (s), 52.1 (q), 50.7 (t), 28.4 (t), 27.9 (t), 21.2 (t). **Enol Form.** $^1$H NMR ($CDCl_3$): $\delta$ 8.77 (s, 1H), 6.50 (t, 1H, $J$ = 4.7 Hz), 6.09 (s, 1H), 5.07 (s, 1H), 2.20 (dt, 2H, $J$ = 6.3, 4.7 Hz), 1.68 (qi, 2H, $J$ = 6.3 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 173.1 (s), 171.0 (s), 143.2 (s), 138.7 (d), 123.1 (s), 122.4 (d), 93.3 (d), 51.1 (q), 28.21 (t), 28.0 (t), 21.7 (t). IR ($CHCl_3$, cm$^{-1}$): 1720 (s). MS (*m/z*, rel intensity): 275 (M$^+$, 7), 273 (M$^+$, 7), 241 (5), 225 (10), 193 (100). Exact mass calcd for $C_{11}H_{13}O_3{}^{79}Br$ 272.0048, found 272.0038.

**(*E*)-2-Bromo-1-{4-oxo-2,2-(ethylenedioxy)-1-butylidene}-2-cyclohexene (35).** A mixture of ester **34** (1.5 g, 5.5 mmol), dry benzene (60 mL), ethylene glycol (3 mL, 0.054 mol), and *p*-toluenesulfonic acid monohydrate (0.1 g, 0.5 mmol) was heated at reflux with azeotropic removal of water (Dean–Stark trap) for 36 h. The reaction was cooled to room temperature, triethylamine (2 mL) was added, and the reaction was stirred for 30 min. The mixture was filtered through a cake of silica gel (15g) over anhydrous magnesium sulfate (5 g) washing with dichloromethane (150 mL). Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (3:1) gave (*E*)-2-bromo-1-{3-carbomethoxy-2,2-(ethylenedioxy)-1-propylidene}-2-cyclohexene as a colorless oil (1.52 g, 87%). $^1$H NMR ($CDCl_3$): $\delta$ 6.32 (t, 1H, $J$ = 4.5 Hz), 5.91 (s, 1H), 3.96–3.83 (m, 4H), 3.64 (s, 3H), 2.82 (s, 2H), 2.69 (m, 2H), 2.18 (dt, 2H, $J$ = 6.2, 4.5 Hz), 1.67 (qi, 2H, $J$ = 6.2 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 169.2 (s), 136.7 (s), 134.9 (d), 130.1 (d), 123.2 (s), 107.0 (s), 64.5 (t), 64.5 (t), 51.8 (q), 43.8 (t), 28.1

(t), 26.6 (t), 21.8 (t). IR ($CHCl_3$, $cm^{-1}$): 1736 (s), 1632 (w). MS (*m/z*, rel intensity): 318 ($M^+$, $^{81}Br$, 53), 316 ($M^+$, $^{79}Br$, 53), 245 (100), 243 (100). Exact mass calcd for $C_{13}H_{17}O_4{}^{81}Br$ 318.0290, found 318.0293; calcd for $C_{13}H_{17}O_4{}^{79}Br$ 316.0310, found 316.0309. Anal. Calcd for $C_{13}H_{17}O_4Br$: C, 49.23; H, 5.40; Br, 25.19. Found: C, 49.27; H, 5.42; Br, 25.16.

To a solution of the protected β-keto ester (1.27 g, 4.0 mmol) in dry toluene (30 mL) at −78 °C was added dropwise DIBAL-H (3.67 mL, 1.2 M in hexene, 4.4 mmol). The reaction mixture was stirred for 30 min followed by quenching at −78 °C with water (2 mL). The solution was allowed to warm up to room temperature after which time a sodium hydroxide solution (15% w/v, 4 mL) was added and the resulting mixture stirred for 15 min. The aqueous layer was separated and extracted with diethyl ether (3 × 10 mL), and the organic layers were combined, washed with brine (20 mL) and water (20 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (3:1) gave compound **35** as a colorless oil (0.80 g, 70%). $^1H$ NMR ($CDCl_3$): δ 9.70 (t, 1H, $J$ = 2.9 Hz), 6.37 (t, 1H, $J$ = 4.5 Hz), 5.89 (s, 1H), 4.02–3.90 (m, 4H), 2.80 (d, 2H, $J$ = 2.9 Hz), 2.73 (m, 2H), 2.19 (dt, 2H, $J$ = 6.1, 4.5 Hz), 1.69 (qi, 2H, $J$ = 6.1 Hz). $^{13}C$ NMR ($CDCl_3$): δ 199.8 (s), 137.6 (s), 135.4 (d), 129.8 (d), 122.9 (s), 104.9 (s), 64.5 (t), 64.5 (t), 50.9 (t), 28.2 (t), 26.7 (t), 21.9 (t). IR ($CHCl_3$, $cm^{-1}$): 1740 (s), 1650 (w). MS (*m/z*, rel intensity): 288 ($M^+$, 5), 286 ($M^+$, 4), 245 (100), 243 (97). Exact mass calcd for $C_{12}H_{15}O_3{}^{79}Br$ 286.0205, found 286.0214; calcd for $C_{10}H_{12}O_2{}^{81}Br$ 245.0000, found 245.0003.

**(+)-(4*R*,5*S*)-3-{(2*R*,3*S*)-(*E*)-6-(2-Bromo-1-cyclohexanylidene)-5,5-(ethylenedioxy)-3-hydroxy-2-methylhexanoyl}-4-methyl-5-phenyl-2-oxazolidinone (37).** A 200 mL, 2-neck round-bottom flask was charged with oxazolidinone **36** (1.68 g, 7.2 mmol) in dry dichloromethane (20 mL). The solution was cooled to −78 °C and stirred for 10 min. Then triethylamine (0.95 g, 1.31 mL, 9.4 mmol) was added to the solution followed by di-*n*-butylboron triflate, and the resulting solution was allowed to warm to 0 °C over 1 h and stirred at 0 °C for an additional 1 h. A solution of aldehyde **35** (2.07 g, 7.2 mmol) in dry dichloromethane (20 mL) was added dropwise and stirring was continued for 1 h. A pH 7.4 buffer (phosphate) (10 mL) was added to the reaction mixture followed by an ice-cold mixture of 30% hydrogen peroxide (15 mL), methanol (30 mL), and the same buffer (15 mL) while stirring was continued for 1 h. Then a solution of saturated aqueous sodium bicarbonate was added slowly to the cold mixture while stirring vigorously for 20 min. The aqueous phase was then separated and extracted with dichloromethane (3 × 30 mL). The organic phases were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (1:1) gave the aldol adduct **37** as a viscous oil (2.91 g, 77%). $^1H$ NMR ($CDCl_3$): δ 7.63–7.22 (m, 5H), 6.29 (t, 1H, $J$ = 4.6 Hz), 5.80 (s, 1H), 5.61 (d, 1H, $J$ = 7.2 Hz), 4.70 (dq, 1H, $J$ = 7.2, 6.6 Hz), 4.15 (m, 1H), 3.99–3.75 (m, 5H), 3.57 (bs, 1H, $D_2O$ exchangeable), 2.67 (m, 2H), 2.15 (dt, 2H, $J$ = 5.8, 4.6 Hz), 2.01 (m, 2H), 1.64 (qi, 2H, $J$ = 5.8 Hz), 1.18 (d, 3H, $J$ = 7.0 Hz), 0.81 (d, 3H, $J$ = 6.6 Hz). $^{13}C$ NMR ($CDCl_3$): δ 175.2 (s), 152.5 (s), 136.8 (s), 134.7 (d), 133.1 (s), 130.5 (d), 128.4 (d), 125.4 (d), 124.4 (d), 123.0 (s), 109.4 (s), 78.6 (d), 68.5 (d), 64.0 (t), 63.7 (t), 54.7 (d), 42.4 (d), 40.5 (t), 28.0 (t), 26.3 (t), 21.7 (t), 14.1(q) 12.0 (q). IR ($CHCl_3$, $cm^{-1}$): 3500 (br), 1760 (s), 1670 (s). MS (*m/z*, rel intensity): 522 (M + 1, 40), 520 (M + 1, 40), 504 (80), 502 (100). Anal. Calcd for $C_{25}H_{30}O_6BrN$: C, 57.79; H, 5.82; N, 2.70. Found: C, 57.74; H, 5.88; N, 2.77. $[\alpha]^{25}_D$ = +11.03° (*c* 0.68, $CHCl_3$).

**(−)-(*E*)-2-Bromo-1-{(2*R*,3*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2,2-(ethylenedioxy)-6-hydroxy-5-methyl-1-hexylidene}-2-cyclohexene (38).** A solution of the secondary alcohol **37** (3.40 g, 6.5 mmol) in dichloromethane (30 mL) and *tert*-butyldimethylsilyl triflate (1.72 g, 6.5 mmol) was cooled to 0 °C and stirred for 10 min before the dropwise addition of triethylamine (0.66 g, 0.91 mL, 6.5 mmol). The resulting mixture was allowed to stir for 30 min and then it was quenched at the same temperature with a solution of saturated sodium bicarbonate (5 mL). The layers were separated, the aqueous layer was extracted with dichloromethane (3 × 15 mL), and the combined organic layers were washed with brine (20 mL) and water (20 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (3:1) gave (−)-(4*R*,5*S*)-{(2*R*,3*S*)-(*E*)-6-(2-bromo-1-cyclohexanylidene)-5,5-(ethylenedioxy)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylhexanoyl}-4-methyl-5-phenyl-2-oxazolidinone as a viscous oil (3.25 g, 79%). $^1H$ NMR ($CDCl_3$): δ 7.42–7.24 (m, 5H), 6.33 (t, 1H, $J$ = 4.4 Hz), 5.88 (s, 1H), 5.58 (d, 1H, $J$ = 6.7 Hz), 4.67 (qi, 1H $J$ = 6.7 Hz), 4.30 (m, 1H), 4.1 (m, 1H), 4.04–3.95 (m, 2H), 3.83–3.77 (m, 2H), 2.71 (m, 2H), 2.27 (dd, 1H, $J$ = 15.2, 8.1 Hz), 2.19 (dt, 2H, $J$ = 5.8, 4.4 Hz), 1.98 (dd, 1H, $J$ = 15.2, 3.2 Hz), 1.69 (qi, 2H, $J$ = 5.8 Hz), 1.18 (d, 3H, $J$ = 6.9 Hz), 0.87 (d, 3H, $J$ = 6.7 Hz), 0.86 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H). $^{13}C$ NMR ($CDCl_3$): δ 175.0 (s), 152.1 (s), 136.3 (s), 134.3 (d), 133.4 (s), 132.1 (d), 128.6 (d), 125.6 (d), 123.6 (s), 108.2 (s), 78.7 (d), 68.6 (d), 63.9 (t), 63.8 (t), 55.4 (d), 43.8 (d), 42.5 (t), 28.3 (t), 26.5 (t), 25.8 (q), 22.0 (t), 18.0 (s), 14.2 (q), 11.1 (q), −4.3 (q), −5.1 (q). IR ($CHCl_3$, $cm^{-1}$): 1780 (s), 1706 (s), 1454 (ms). MS (*m/z*, rel intensity): 636 (M + 1, 10), 634 (M + 1, 10), 620 (20), 618 (20), 578 (20), 576 (20), 504 (100), 502 (100). Anal. Calcd for $C_{31}H_{44}O_6BrNSi$: C, 58.67; H, 6.99; N, 2.21. Found: C, 58.47; H, 6.77; N, 2.08. $[\alpha]^{25}_D$ = −9.70° (*c* 1.34, $CHCl_3$).

To a solution of the above oxazolidinone (0.45 g, 0.71 mmol) in THF (50 mL) at 0 °C was added dropwise a solution of lithium borohydride (0.046 g, 2.1 mmol) in THF (10 mL). The reaction mixture was allowed to warm up slowly to 4 °C and was stirred at that temperature for 10 days. A saturated solution of ammonium chloride (5 mL) was added dropwise to the reaction mixture while stirring continued for another 20 min. The aqueous layer was separated and extracted three times with diethyl ether (15 mL each). The organic layers were combined, washed with brine (15 mL) and water (15 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography on Florisil eluting with hexanes–ethyl acetate (3:1) gave **38** as a colorless oil (0.27 g, 83%). The product is unstable and decomposes slowly at room temperature. $^1H$ NMR ($CDCl_3$): δ 6.35 (t, 1H, $J$ = 4.5 Hz), 5.88 (s, 1H), 4.10 (m, 1H), 4.0–3.8 (m, 4H), 3.52 (m, 2H), 2.75 (m, 2H), 2.3–2.2 (m, 2H), 2.1–2.0 (m, 2H), 1.8–1.7 (m, 2H), 0.99 (s, 9H), 0.82 (d, 3H, $J$ = 6.8 Hz), 0.15 (s, 3H), 0.10 (s, 3H). IR ($CHCl_3$, $cm^{-1}$): 3638 (w), 3500–3470 (bw), 1726 (s). $[\alpha]^{25}_D$ = −13.0° (*c* 1.46, $CHCl_3$).

**(−)-(*E*)-1-{(2*R*,3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,2-(ethylenedioxy)-6-hydroxy-5-methyl-1-hexylidene}-2-formyl-2-cyclohexene (39).** A 25 mL round-bottom flask was charged with a solution of alcohol **38** (0.116 g, 0.25 mmol) in THF (5 mL). The mixture was cooled to −78 °C (dry ice–acetone bath) and stirred for 10 min before the dropwise addition of *n*-BuLi (2.5 M solution in hexane, 0.20 mL, 0.50 mmol). The mixture was stirred for 1 h and then DMF (0.056 g, 0.77 mmol) was added in a dropwise fashion. The resulting mixture was stirred for an additional 2 h and then quenched with a solution of saturated ammonium chloride (2 mL) at −78 °C. The reaction mixture was allowed to warm up to room temperature and was then acidified with hydrochloric acid (1 N solution in water, 1 mL). The aqueous layer was separated and extracted with diethyl ether (3 × 5 mL), and the organic layers were combined and washed with brine (5 mL) and water (5 mL). Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (2:1) gave compound **39** as a colorless oil (0.062 g, 60% yield) and starting material (0.029 g). $^1H$ NMR ($CDCl_3$): δ 9.45 (s, 1H), 6.73 (t, 1H, $J$ = 4.1 Hz), 6.54 (s, 1H), 4.09 (m, 1H), 3.9–3.8 (m, 4H), 3.52 (m, 2H), 2.58 (m, 2H), 2.45 (m, 2H), 2.15 (dd, 2H, $J$ = 14.7, 7.6 Hz), 1.99 (m, 1H), 1.94 (dd, 2H, $J$ = 14.7, 3.9 Hz), 1.72 (m, 2H), 0.84 (s, 9H), 0.80 (d, 1H, $J$ = 6.8 Hz), 0.0.06 (s, 3H), 0.04 (s, 3H). $^{13}C$ NMR ($CDCl_3$): δ 193.4 (d), 154.6 (d), 137.9 (s), 132.3 (s), 130.4 (d), 108.8 (s), 69.7 (d), 66.20 (t), 64.0 (t), 63.7 (t), 42.2 (t), 40.3 (d), 27.2 (t), 25.8 (t), 25.5 (q), 21.9 (t), 18.0 (s), 10.4 (q), −4.2 (q), −4.8 (q). IR ($CHCl_3$, $cm^{-1}$): 3500 (bw), 1692 (ms), 1604 (w). MS (*m/z*, rel intensity): 410 ($M^+$, 5), 396 (40), 377 (20), 349 (100). Exact mass calcd for $C_{22}H_{38}O_5Si$ 410.2488, found 410.2497. Anal. Calcd for $C_{22}H_{38}O_5Si$: C,

64.35; H, 9.34; O, 19.49. Found: C, 64.52; H, 9.44; O, 19.61. $[\alpha]^{25}_D = -12.8°$ (c 1.33, $CHCl_3$).

**(*E*)-(4*R*,6*R*)-10- and (*E*)-(4*S*,6*S*)-10-{(2*S*,3*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,2-(ethylenedioxy)-6-hydroxy-5-methyl-1-hexylidene}-4-ethoxy-3-oxabicyclo[4.4.0]non-1-ene (40a and 40b).** To a mixture of aldehyde alcohol **39** (0.334 g, 8.14 mmol) in ethyl vinyl ether (5 mL) was added $Yb(FOD)_3$ (0.1 g, 0.977 mmol). The reaction was allowed to stir under an argon atmosphere at room temperature for 10 days. Evaporation of the excess ethyl vinyl ether *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (3:1) gave a 1:1 mixture of two isomeric compounds **40a** and **40b** as a colorless oil (0.31 g, 80%). Many NMR signals in the spectra of the two isomers were distinguishable. However, it was impossible to assign the resonances to a particular isomer. $^1H$ NMR ($(CD_3)_2CO$): $\delta$ 6.44 (d, 1H, $J$ = 1.6 Hz), 6.39 (d, 1H, $J$ = 1.6 Hz), 5.24 (d, 1H, $J$ = 1.9 Hz), 5.23 (d, 1H, $J$ = 1.9 Hz), 4.82 (dd, 1H, $J$ = 9.5, 2.1 Hz), 4.80 (dd, 1H, $J$ = 9.5, 2.1 Hz), 4.20 (m, 1H), 4.18 (m, 1H), 3.9–3.1 (m, 18H), 2.4–1.1 (m, 24H), 1.15 (t, 6H, $J$ = 6.0 Hz), 0.862 (s, 9H), 0.860 (s, 9H), 0.804 (d, 3H, $J$ = 6.7 Hz), 0.802 (d, 3H, $J$ = 6.7 Hz), 0.10 (s, 3H), 0.07 (s, 3H), 0.060 (s, 3H), 0.055 (s, 3H). $^{13}C$ NMR ($(CD_3)_2CO$): $\delta$ 140.6 (s), 140.4 (s), 136.8 (d), 136.7 (d), 123.9 (d), 123.7 (d), 120.1 (s), 119.9 (s), 109.1 (s), 108.9 (s), 100.4 (d), 100.4 (d), 68.8 (d), 68.5 (d), 65.6 (t), 65.4 (t), 65.3 (t), 64.8 (t), 64.7 (t), 64.6 (t), 64.3 (t), 64.1 (t), 44.5 (t), 44.5 (t), 41.4 (d), 40.8 (d), 37.2 (t), 37.2 (t), 34.8 (d), 34.8 (d), 33.9 (t), 33.8 (t), 28.9 (t), 28.8 (t), 26.3 (q), 26.3 (q), 25.8 (t), 25.7 (t), 18.7 (s), 18.7 (s), 15.5 (q), 15.5 (q), 9.8 (q), 9.6 (q), −3.9 (q), −4.0 (q), −4.7 (q);−4.7 (q). IR ($CH_2Cl_2$, $cm^{-1}$): 3460 (bm), 1735 (s), 1613 (w). MS ($m/z$, rel intensity): 483 (M + 1, 4), 421 (15), 375 (11), 289 (21), 112(100). Exact mass calcd for $C_{26}H_{46}O_6Si$ 482.3064, found 482.3051. Anal. Calcd for $C_{26}H_{46}O_6Si$: C, 64.69; H, 9.61. Found: C, 64.32; H, 9.70.

**(−)-$\Delta^{9,17}$-(1*R*,3*R*,5*R*,10*S*,13*S*,14*S*,15*S*,16*R*)-, (+)-$\Delta^{9,17}$-(1*S*,3*R*,5*R*,10*R*,13*S*,14*S*,15*S*,16*R*)-, and (−)-$\Delta^{9,17}$-(1*R*,3*S*,5*S*,10*S*,13*S*,14*S*,15*S*,16*R*)-3-ethoxy-16-carbomethoxy-14-methyl-13-[(*tert*-butyldimethylsilyl)oxy]-11,11-(ethylenedioxy)-2-oxatetracyclo[7.7.1.0$^{5,17}$.0$^{10,15}$]heptadec-9-ene (42a, 42b, and 42c).** To a mixture of the Dess–Martin periodinane (0.08 g, 0.20 mmol) in dichloromethane (10 mL) at room temperature was added pyridine (0.15 mL, 1.9 mmol). The reaction mixture was allowed to stir for 10 min before the dropwise addition of the mixture of alcohols **40** (0.095 g, 0.20 mmol). Stirring was continued for an extra 45 min. The reaction mixture was cooled to 0 °C and a mixture of $Na_2S_2O_3$ (5% solution, 7 mL), a saturated solution of sodium bicarbonate (12 mL) was added, and stirring was continued for 1 h. The solution was diluted with diethyl ether (5 mL), the aqueous layer was separated and extracted three times with diethyl ether (5 mL each). The organic layers were combined, washed with water (10 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (5:1) afforded (*E*)-(4*R*,6*R*)-10- and (*E*)-(4*S*,6*S*)-10-{(2*R*,3*S*)-4-[(*tert*-butyldimethylsilyl)-oxy]-2,2-(ethylenedioxy)-6-oxo-5-methyl-1-hexylidene}-4-ethoxy-3-oxabicyclo[4.4.0]dec-1-ene as a colorless oil (0.074 g, 82%). $^1H$ NMR ($(CD_3)_2CO$): $\delta$ 9.62 (d, 2H, $J$ = 0.5 Hz), 6.40 (d, 1H, $J$ = 1.6 Hz), 6.39 (d, 1H, $J$ = 1.6 Hz), 5.27 (bs, 2H), 4.82 (d, 2H, $J$ = 9.4 Hz), 4.60 (m, 2H), 4.0–3.1 (m, 12H), 2.68 (qm, 2H, $J$ = 6.9 Hz), 2.4–1.1 (m, 22H), 1.17 (t, 6H, $J$ = 6.0 Hz), 1.06 (d, 3H, $J$ = 7.2 Hz), 1.05 (d, 3H, $J$ = 7.2 Hz), 0.81 (s, 18H), 0.10 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H). IR ($CHCl_3$, $cm^{-1}$): 2840 (w), 1715 (w). MS ($m/z$, rel intensity): 482 ($M^+$, 17), 481 (58), 480 (11), 479 (13), 465 (30), 435 (100). Exact mass calcd for $C_{26}H_{44}O_6Si$ 480.2907, found 480.2879. Anal. Calcd for $C_{26}H_{44}O_6Si$: C, 64.96; H, 9.23. Found: C, 64.91; H, 9.41.

Methyl diethylphosphonoacetate (0.51 mL, 0.47 M solution in benzene, 0.24 mmol) was added slowly to a suspension of sodium hydride (5.6 mg, 0.24 mmol) in dry THF (5 mL) at 0 °C. The reaction mixture was stirred for 1 h and then added to a solution of the above aldehydes (94 mg, 0.20 mmol) in THF (4 mL) via a canula. After stirring for 2 h at 0 °C, the reaction was quenched with water (1 mL). Then the mixture was washed with a saturated aqueous solution of ammonium chloride (7 mL). The aqueous layer was separated and extracted with diethyl ether. The combined organic portions were washed with brine (5 mL) and dried over anhydrous magnesium sulfate. Removal of solvent *in vacuo* followed by flash column chromatography eluting with hexanes–ethyl acetate (6:1) yielded (*E*)-(4*R*,6*R*)-10- and (*E*)-(4*S*,6*S*)-10-{(*E*)-(3*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2,2-(ethylenedioxy)-7-carbomethoxy-5-methylhept-6-en-1-ylidene}-4-ethoxy-3-oxabicyclo[4.4.0]dec-1-ene as a colorless oil (105 mg, 100%) which could be isolated for the purpose of identification. $^1H$ NMR ($(CD_3)_2CO$): $\delta$ 7.0 (dd, 2H, $J$ = 15.0, 6.5 Hz), 6.40 (d, 2H, $J$ = 1.6 Hz), 5.80 (d, 2H, $J$ = 15.0 Hz), 5.24 (bs, 2H), 4.82 (d, 2H, $J$ = 9.4 Hz), 4.0–3.1 (m, 14H), 3.82 (s, 6H), 2.75 (m, 2H), 2.4–1.1 (m, 22H), 1.17 (t, 6H, $J$ = 6.0 Hz), 1.06 (d, 3H, $J$ = 7.2 Hz), 1.05 (d, 3H, $J$ = 7.2 Hz), 0.81 (s, 18H), 0.05 (s, 6H), 0.03 (s, 6H).

This product was then dissolved in acetone-$d_6$ or $CDCl_3$ and transferred to an NMR tube. Immersing the NMR tube in a water bath at 39 °C for 24 h and monitoring by proton NMR revealed three new ester peaks. After the complete disapearance of the olefin signals of the $\alpha,\beta$-unsaturated ester, careful integration of the new signals at 2.8 and 2.9 ppm ($C_6$) revealed a 1:1.7 ratio of **42a** and **42c**. The crude product was then purified by flash column chromatography eluting with hexanes–ethyl acetate (9:1) to yield three tetracyclic products **42a**:**42b**:**42c** in a 1.5:1:1.6 isolated ratio. Thus the true ratio works out to be 1.5:1:2.4. The three products were identified as **42a** (30 mg), **42b** (20 mg), and **42c** (32 mg) for a combined isolated yield of 89%. **Tetracycle 42a.** $^1H$ NMR ($(CD_3)_2CO$): $\delta$ 4.53 (dd, 1H, $J$ = 1.8, 9.6 Hz), 3.99 (bs, 4H), 3.96 (dm, 1H, $J$ = 7.6 Hz), 3.75 (dq, 1H, $J$ = 7.5, 10.0 Hz), 3.61 (s, 3H), 3.39 (dq, 1H, $J$ = 7.5, 10.0 Hz), 3.38 (m, 1H), 2.81 (dd, 1H, $J$ = 2.2, 9.0 Hz), 2.38 (m, 1H), 2.27 (m, 2H), 2.16 (dd, 1H, $J$ = 4.7, 17.8 Hz), 1.81 (ddd, 1H, $J$ = 2.0, 4.2, 12.1 Hz), 1.80–1.50 (m, 2H), 1.47 (dd, 1H, $J$ = 10.7, 17.8 Hz), 1.4–1.0 (m, 4H), 1.10 (t, 3H, $J$ = 7.5 Hz), 0.90 (d, 3H, $J$ = 6.9 Hz), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). $^{13}C$ NMR ($(CD_3)_2CO$): $\delta$ 173.6 (s), 131.5 (s), 131.0 (s), 111.6 (s), 101.7 (d), 73.7 (d), 70.9 (d), 64.5 (t), 63.8 (t), 63.6 (t), 51.2 (d), 50.0 (d), 49.0 (d), 47.5 (d), 45.6 (t), 40.7 (t), 38.2 (q), 36.3 (q), 31.0 (t), 29.2 (t), 26.2 (q), 23.6 (t), 18.5 (s), 16.0 (q), 15.5 (q), −4.1 (q), −4.6 (q). IR ($CHCl_3$, $cm^{-1}$): 1730 (w), 1070 (s). MS ($m/z$, rel intensity): 537 (M + 1, 2), 535 (6), 521 (5), 491 (38), 435 (16), 404 (13), 126 (100). Exact mass calcd for $C_{29}H_{48}O_7Si$ 536.3169, found 536.3166. Anal. Calcd for $C_{29}H_{48}O_7Si$: C, 64.89; H, 9.02. Found: C, 65.01; H, 9.12. $[\alpha]^{25}_D = -9.8°$ (c 0.52, $CHCl_3$). **Tetracycle 42b.** $^1H$ NMR ($CDCl_3$, −30 °C): $\delta$ 4.96 (t, 1H, $J$ = 6.9 Hz), 2.55 (d, 1H, $J$ = 10 Hz), 3.96–3.86 (m, 4H), 3.69 (s, 3H), 3.64–3.57 (m, 1H), 3.5 (dd, 1H, $J$ = 14.0, 7.1 Hz), 3.38–3.30 (m, 1H), 2.23–2.13 (m, 5H), 1.96–1.87 (m, 3H), 1.77–1.71 (m, 5H), 1.40–1.36 (m, 1H), 1.20–1.16 (m, 1H), 1.14 (t, 3H, $J$ = 7.1 Hz), 0.96–0.91 (m, 3H), 0.82 (s, 9H), 0.01 (S, 6H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 176.5 (s), 135.1 (s), 126.0 (s), 97.3 (d), 73.2 (d), 68.3 (d), 64.6 (t), 63.3 (t), 62.5 (t), 52.2 (d), 50.6 (d), 43.7 (d), 42.7 (d), 42.6 (t), 40.6 (d), 36.0 (t), 28.6 (q), 28.5 (t), 26.5 (t), 25.9 (q), 25.7 (q), 22.3 (t), 19.1 (s), 15.1 (q), 14.8 (q), −4.4 (q), −4.9 (q). IR ($CHCl_3$, $cm^{-1}$): 1727 (w), 1060 (s). MS ($m/z$, rel intensity): 537 (M + 1, 2), 535 (6), 521 (6), 126 (100). $[\alpha]^{25}_D = +8.4°$ (c 0.37, $CHCl_3$). **Tetracycle 42c.** $^1H$ NMR ($CDCl_3$): $\delta$ 4.90 (t, 1H, $J$ = 7.0 Hz), 4.27 (d, 1H, $J$ = 8.0 Hz), 4.10–4.07 (m, 1H), 4.04–3.92 (m, 4H), 3.81 (dd, 1H, $J$ = 7.1, 2.7 Hz), 3.60(s, 3H), 3.44 (dd, 1H, $J$ = 9.8, 7.1 Hz), 3.33–3.26 (m, 1H), 2.88, (dd, 1H, $J$ = 8.2, 5.5 Hz), 2.27 (br d, 1H), 2.14–1.99 (m, 5H), 1.75–1.65 (m, 2H), 1.63–1.57 (m, 1H), 1.53–1.47 (m, 1H), 1.37 (dd, 2H, $J$ = 12.8, 11.5 Hz), 1.17 (t, 3H, $J$ = 7.1 Hz), 1.08 (m, 1H), 1.00 (d, 3H, $J$ = 6.4 Hz), 0.86 (s, 9H), 0.01 (s, 6H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 175.2 (s), 134.8 (s), 127.8 (s), 109.7(s), 97.6 (d), 73.0 (d), 65.8 (d), 63.3 (t), 62.8 (t), 51.5 (d), 50.6 (d), 45.8 (d), 44.5 (d), 42.9 (d), 42.8 (t), 36.5 (t), 29.8 (q), 28.9 (t), 25.8 (q), 25.2 (t), 22.9 (t) 18.0 (s), 15.8 (q), −4.3 (q), −4.7 (q). IR ($CHCl_3$, $cm^{-1}$): 1730 (w), 1070 (s). MS ($m/z$, rel intensity): 537 (M + 1, 2.1), 535 (6), 521 (5), 491 (39), 126 (100). $[\alpha]^{25}_D = -37°$ (c 0.5, $CHCl_3$).

**2-Bromo-4-methyl-2-cyclohexen-1-one (44).** Bromine (1.45 g, 9.1 mmol) in dry carbon tetrachloride (15 mL) was added dropwise to a solution of 4-methyl-2-cyclohexen-1-one (**43**) (1.01 g, 9.1 mmol) in dry carbon tetrachloride (15 mL) at

−10 °C. The reaction mixture was stirred for 10 min at −10 °C and then warmed to 0 °C and triethylamine (1.59 g, 15.7 mmol) in dry carbon tetrachloride (10 mL) was added slowly. The reaction mixture was stirred for 3 h at 0 °C and filtered, washing with carbon tetrachloride. The filtrate was washed with one portion of 1 N hydrochloric acid (20 mL) and one portion of saturated aqueous sodium bicarbonate (20 mL). The aqueous layers were extracted separately with diethyl ether (2 × 20 mL), and the combined organic portions were washed with saturated sodium chloride (20 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by flash column chromatography eluting with hexanes–ethyl acetate (4:1) to give 1.11g (64%) of bromo ketone **44** as a colorless oil. $^1$H NMR ($CDCl_3$): δ 7.23 (d, 1H, $J$ = 2.4 Hz), 3.50–3.37 (m, 2H), 3.28 (ddd, 1H, $J$ = 14.0, 10.4, 4.0 Hz), 3.01–2.91 (m, 1H), 2.69–2.56 (m, 1H), 2.17 (d, 3H, $J$ = 6.0 Hz). $^{13}$C NMR ($CDCl_3$): δ 156.4 (d), 123.1 (s), 115.1 (s), 36.9 (t), 34.2 (d), 30.6 (t), 20.0 (q). IR ($CHCl_3$, cm$^{-1}$): 1695 (s) 1595 (ms). MS (*m/z*, rel intensity): 190 (68, $M^+$, $^{81}$Br), 188 (64, $M^+$, $^{79}$Br), 109 (72), 81 (100). Exact mass calcd for $C_7H_9OBr$ 187.9837, found 187.9833.

**2-Bromo-4-methyl-1-vinyl-2-cyclohexen-1-ol (45a).** 2-Bromo-4-methyl-2-cyclohexen-1-one (**44**) (1.06 g, 5.6 mmol) in diethyl ether (10 mL) and vinylmagnesium bromide (1 M in THF, 17 mL) in diethyl ether (100 mL) were treated as per bromo ketone **18**. The product was then purified by flash column chromatography eluting with hexanes–ethyl acetate (3:1) to yield 773 mg and 256 mg (84%) of two stereoisomers of **45a**. **Major Isomer.** $^1$H NMR ($CDCl_3$): δ 6.09 (dd, 1H, $J$ = 2.8, 1.0 Hz), 5.84 (dd, 1H, $J$ = 17.3, 10.6 Hz), 5.26 (dd, 1H, $J$ = 17.3, 1.0 Hz), 5.22 (dd, 1H, $J$ = 10.6, 1.0 Hz), 2.33 (m, 1H), 2.24 (s, 1H), 2.01 (ddd, 1H, $J$ = 13.0, 5.4, 3.1 Hz), 1.89 (dt, 1H, $J$ = 13.0, 3.1 Hz), 1.80 (m, 1H), 1.29 (m, 1H), 1.00 (d, 3H, $J$ = 7.1 Hz). $^{13}$C NMR ($CDCl_3$): δ 141.5 (d), 138.5 (d), 128.0 (s), 115.7 (t), 74.7 (s), 31.6 (t), 27.7 (d), 22.6 (t), 14.1 (q). IR ($CHCl_3$, cm$^{-1}$): 3620–3500 (br), 1635 (w). MS (*m/z*, rel intensity): 217 ($M^+$ − 1, $^{81}$Br), 215 ($M^+$ − 1, $^{79}$Br), 201 (100), 199 (97). Anal. Calcd for $C_9H_{13}BrO$: C, 50.0; H, 6.07; O, 7.40; Br, 36.53. Found: C, 49.96; H, 6.15; Br, 36.51. **Minor Isomer.** $^1$H NMR ($CDCl_3$): δ 6.11 (d, 1H, $J$ = 3.0 Hz), 5.82 (dd, 1H, $J$ = 17.2, 10.6 Hz), 5.34 (dd, 1H, $J$ = 17.2, 1.1 Hz), 5.20 (dd, 1H, $J$ = 10.6, 1.1 Hz), 2.27 (m, 1H), 2.21 (s, 1H), 1.99 (ddd, 1H, $J$ = 14.1, 7.9, 3.2 Hz), 1.84–1.71 (m, 2H), 1.45 (m, 1H), 1.05 (d, 3H, $J$ = 7.1 Hz). $^{13}$C NMR ($CDCl_3$): δ 142.7 (d), 138.7 (d), 127.9 (s), 114.3 (t), 74.0 (s), 35.8 (t), 33.6 (d), 26.7 (t), 20.4 (q).

**(*E*)-2-Bromo-6-methyl-3-{1-propylidene}-1-cyclohexene (48a).** Acetic anhydride (0.94 g, 9.3 mmol), alcohol **45a** (1.01 g, 4.7 mmol), DMAP (0.11 g, 0.93 mmol), and triethylamine (1.18 g, 11.6 mmol) were treated as per compound **19**. Flash chromatography eluting with hexanes–ethyl acetate (9:1) produced 0.85 g of 1-acetoxy-2-bromo-4-methyl-1-vinyl-2-cyclohexene (70%). $^1$H NMR ($CDCl_3$): δ 6.14 (dd, 1H, $J$ = 2.3, 1.2 Hz), 5.88 (dd, 1H, $J$ = 17.5, 10.6 Hz), 5.28 (dd, 1H, $J$ = 17.5, 0.9 Hz), 5.28 (dd, 1H, $J$ = 10.6, 0.9 Hz), 2.62 (ddd, 1H, $J$ = 14.1, 12.7, 1.4 Hz), 2.47–2.36 (m, 1H), 2.07 (s, 3H), 2.01 (dt, 1H, $J$ = 14.1, 1.4 Hz), 1.82–1.74 (m, 1H), 1.37–1.26 (m, 1H), 1.00 (d, 3H, $J$ = 7.1 Hz). IR ($CHCl_3$, cm$^{-1}$): 1740 (s), 1640 (w). MS (*m/z*, rel intensity): 261 (2, M + 1, $^{81}$Br), 259 (2, M + 1, $^{79}$Br), 201 (100), 199 (99), 137 (53).

Methyllithium (1.4 M in diethyl ether, 8.8 mL, 12.4 mmol) was added to a suspension of dry cuprous iodide (1.18 g, 6.2 mmol) in diethyl ether (30 mL) at 0 °C. A solution of the above acetate (0.80 g, 3.1 mmol) in diethyl ether (30 mL) was then added to this clear solution of lithium dimethylcuprate, and a yellow precipitate appeared immediately. The reaction mixture was stirred for 40 min at 0 °C and then quenched with saturated aqueous ammonium chloride (40 mL). The aqueous phase was separated and extracted with diethyl ether (2 × 15 mL). The combined organic layers were washed with saturated aqueous sodium chloride (30 mL) and dried over anhydrous magnesium sulfate. Evaporation of solvent *in vacuo* followed by flash chromatography eluting with hexanes–ethyl acetate (15:1) yielded **48a** as a colorless oil (0.48 g, 72%). $^1$H NMR ($CDCl_3$): δ 6.05 (d, 1H, $J$ = 3.2 Hz), 5.85 (t, 1H, $J$ = 7.3 Hz), 2.62 (dt, 1H, $J$ = 14.9, 4.7 Hz), 2.46–2.35 (m, 1H), 2.23 (bt, 1H, $J$ = 14.0 Hz), 2.12 (dqi, 2H, $J$ = 7.6, 3.2 Hz), 1.88–1.81 (m, 1H), 1.35–1.23 (m, 1H), 1.02 (d, 3H, $J$ = 7.1 Hz), 1.00 (t, 3H, $J$ = 7.6 Hz). IR ($CHCl_3$, cm$^{-1}$): 1590 (w) 1375 (w). MS (*m/z*, rel intensity): 217 (18, M + 1, $^{81}$Br), 215 (23, M + 1, $^{79}$Br), 135 (100). Exact mass calcd for $C_{10}H_{16}Br$ 215.0435, found 215.0439. Anal. Calcd for $C_{10}H_{15}Br$: C, 55.83; H, 7.03. Found: C, 55.76; H, 6.99.

**(*E*)-2-Formyl-6-methyl-3-{1-propylidene}-1-cyclohexene (49a).** Bromide **48a** (0.40 g, 1.8 mmol) in THF (20 mL), *n*-BuLi (2.5 M in hexanes, 1.10 mL, 2.8 mmol) in THF (2 mL), and DMF (0.54 g, 7.4 mmol) were treated as per compound **22**. Flash column chromatography eluting with hexanes–ethyl acetate (15:1) gave **49a** as a colorless oil (0.22 g, 72%). $^1$H NMR ($CDCl_3$): δ 9.47 (s, 1H), 6.62 (t, 1H, $J$ = 7.1 Hz), 6.40 (d, 1H, $J$ = 3.1 Hz), 2.58–2.51 (m, 2H), 2.16–2.06 (m, 3H), 1.91–1.83 (m, 1H), 1.32–1.21 (m, 1H), 1.12 (d, 3H, $J$ = 7.2 Hz), 0.99 (t, 3H, $J$ = 7.5 Hz). $^{13}$C NMR ($CDCl_3$): δ 194.3 (d), 157.1 (d), 137.1 (s), 131.6 (d), 128.1 (s), 32.2 (d), 30.2 (t), 24.2 (t), 21.2 (t), 20.2 (q), 13.9 (q). IR ($CHCl_3$, cm$^{-1}$): 1730 (w), 1690 (s). MS (*m/z*, rel intensity): 164 ($M^+$, 26), 149 (100), 131 (21). Exact mass calcd for $C_{11}H_{16}O$ 164.1202, found 164.1200.

**(−)-(1*S*,6*R*)-3-Bromo-8,8-dimethyl-4-oxo-7,9-dioxabicyclo[4.3.0]non-2-ene (47).** Bromine (3.33 g, 20.8 mmol) in $CCl_4$ (50 mL), ketone **46** (3.50 g, 20.8 mmol) in carbon tetrachloride (50 mL), and triethylamine (3.58 g, 35.4 mmol) in carbon tetrachloride (35 mL) were treated as per compound **17**. The product was purified by flash column chromatography with hexanes–ethyl acetate (2:1) to give **47** as a white solid (3.6 g, 70%): mp 101.5–103.5 °C. $^1$H NMR ($CDCl_3$): δ 7.06 (dd, 1H, $J$ = 3.0, 1.8 Hz), 4.73 (dd, 1H, $J$ = 4.9, 3.0 Hz), 4.69–4.63 (m, 1H), 3.14 (dd, 1H, $J$ = 17.5, 2.6 Hz), 2.77 (dd, 1H, $J$ = 17.5, 3.6 Hz), 1.36 (s, 6H). $^{13}$C NMR ($CDCl_3$): δ 187.3 (s), 146.1 (d), 123.7 (s), 110.0 (s), 73.2 (d), 72.7 (d), 38.4 (t), 27.5 (q), 26.2 (q). IR ($CHCl_3$, cm$^{-1}$): 1700 (s), 1610 (ms). MS (*m/z*, rel intensity): 249 (89, $M^+$ + 1), 247 (100, $M^+$ + 1), 233 (14), 191 (93), 189 (94), 163 (82), 161 (91). Exact mass calcd for $C_9H_{12}O_3Br$ 246.9970, found 246.9965. $[\alpha]_D$ = −18.63° ($CHCl_3$, $c$ = 1.83). Anal. Calcd for $C_9H_{11}O_3Br$: C, 43.75; H, 4.49; Br, 32.34. Found: C, 43.76; H, 4.32; Br, 32.24.

**(−)-(1*S*,6*R*)-3-Bromo-8,8-dimethyl-4-hydroxy-4-vinyl-7,9-dioxabicyclo[4.3.0]non-2-ene (45b).** A solution of *n*-BuLi (1.6 M in hexanes, 6.1 mL, 9.8 mmol) and diethyl ether (50 mL) was added to tetravinyltin (0.62 g, 2.7 mmol) in diethyl ether (10 mL) at 0 °C. The reaction mixture was stirred at rt for 40 min and then bromo ketone **47** (1.22 g, 4.9 mmol) in diethyl ether (50 mL) was added slowly to the solution at −78 °C. The mixture was stirred for 60 min at −78 °C and quenched with saturated aqueous ammonium chloride (60 mL). The aqueous layer was separated and extracted with diethyl ether (2 × 60 mL). The combined organic layers were washed with saturated aqueous sodium chloride (50 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure. The product was then purified by flash column chromatography eluting with hexanes–ethyl acetate (3:1) to yield alcohol **45b** as white crystals (0.71 g, 53%): mp 55–57 °C. $^1$H NMR ($CDCl_3$): δ 6.11 (dd, 1 H, $J$ = 3.1, 1.0 Hz), 5.70 (ddd, 1H, $J$ = 17.1, 10.6, 1.2 Hz), 5.44 (dd, 1H, $J$ = 17.1, 1.3 Hz), 5.23 (dd, 1H, $J$ = 10.6, 1.3 Hz), 4.51 (dd, 1H, $J$ = 8.3, 3.1 Hz), 4.48–4.45 (m, 1H), 3.81 (d, 1H, $J$ = 1.2 Hz), 2.40 (dd, 1H, $J$ = 15.0, 4.5 Hz), 2.11 (dd, 1H, $J$ = 15.0, 2.5 Hz), 1.46 (s, 3H), 1.35 (s, 3H). $^{13}$C NMR ($CDCl_3$): δ 140.8 (d), 131.7 (s), 128.9 (d), 115.1 (t), 110.3 (s), 73.7 (d), 72.4 (s), 72.4 (d), 37.5 (t), 28.0 (q), 26.5 (q). IR ($CHCl_3$, cm$^{-1}$): 3600–3400 (br), 1630 (w). MS (*m/z*, rel intensity): 261 (63, $M^+$ − 15, $^{81}$Br), 259 (63, $M^+$ − 15, $^{79}$Br), 201 (99), 199(95), 137(100). Exact mass calcd for $C_{10}H_{12}O_3Br$ 258.9970, found 258.9975. Anal. Calcd for $C_{11}H_{15}O_3Br$: C, 48.02; H, 5.50; Br, 29.04. Found: C, 47.86; H, 5.68; Br, 28.92. $[\alpha]_D$ = −36.29° ($CHCl_3$, $c$ = 1.78).

**(−)-(*E*)-(1*S*,6*R*)-3-Bromo-8,8-dimethyl-4-propylidene-7,9-dioxabicyclo[4.3.0]non-2-ene (48b).** Acetic anhydride (0.85 g, 8.4 mmol), alcohol **45b** (1.15 g, 4.2 mmol), DMAP (0.10 g, 0.84 mmol), and triethylamine (1.48 g, 14.7 mmol) were treated as per compound **19**. Flash column chromatography eluting with hexanes–ethyl acetate (3:1) produced (+)-(1*S*,6*R*)-

3-bromo-8,8-dimethyl-4-acetoxy-4-vinyl-7,9-dioxabicyclo[4.3.0]-non-2-ene as a white solid (1.25 g, 94%): mp 88.5–90 °C. $^1$H NMR ($CDCl_3$): $\delta$ 6.40 (d, 1H, $J$ = 4.4 Hz), 5.84 (dd, 1H, $J$ = 17.2, 10.7 Hz), 5.29 (d, 1H, $J$ = 10.7 Hz), 5.27 (d, 1H, 17.2 Hz), 4.39 (dd, 1H, $J$ = 6.0, 4.4 Hz), 4.28 (ddd, 1H, $J$ = 10.4, 6.0, 5.0 Hz), 2.83 (dd, 1H, $J$ = 12.4, 10.4 Hz), 2.29 (dd, 1H, $J$ = 12.4, 5.0 Hz), 2.07 (s, 3H), 1.47 (s, 3H), 1.33 (s, 3H). IR ($CHCl_3$, cm$^{-1}$): 1750 (s), 1645 (w). MS (*m/z*, rel intensity): 303 (9, $M^+$, $^{81}$Br), 301 (9, $M^+$, $^{79}$Br), 261 (17), 259 (17), 137 (100). Exact mass calcd for $C_{12}H_{14}O_4Br$ 301.0075, found 301.0062. $[\alpha]_D$ = +60.6° ($CHCl_3$, $c$ = 0.34).

Methyllithium (1.4 M in ether, 10.6 mL, 14.9 mmol), copper iodide (1.42 g, 7.4 mmol) in diethyl ether (60 mL), and the acetate of alcohol **45b** (1.18 g, 3.7 mmol) in diethyl ether (60 mL) were treated as per compound **20**. The product was purified by flash chromatography eluting with hexanes–ethyl acetate (5:1) to yield compound **48b** as a colorless oil (0.50 g, 49%). $^1$H NMR ($CDCl_3$): $\delta$ 6.09 (t, 1H, $J$ = 7.2 Hz), 6.05 (d, 1H, $J$ = 3.6 Hz), 4.54 (t, 1H, $J$ = 4.5 Hz), 4.35 (q, 1H, $J$ = 4.5 Hz), 2.87 (dd, 1H, $J$ = 15.5, 4.9 Hz), 2.51 (bd, 1H, $J$ = 15.5 Hz), 2.16 (qi, 2H, $J$ = 7.2 Hz), 1.38 (s, 3H), 1.34 (s, 3H), 1.02 (t, 3H, $J$ = 7.2 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 137.2 (d), 127.2 (d), 127.1 (s), 126.5 (s), 109.3 (s), 73.5 (d), 72.1 (d), 28.3 (t), 28.0 (q), 26.5 (q), 21.3 (t), 13.7 (q). IR ($CHCl_3$, cm$^{-1}$): 1640 (w), 1605 (w). MS (*m/z*, rel intensity): 274 (53, $M^+$, $^{81}$Br), 272 (51, $M^+$, $^{79}$Br), 259 (69), 257 (64), 216 (43), 214 (42), 91 (100). Exact mass calcd for $C_{12}H_{17}O_2Br$ 272.0412, found 272.0422. Anal. Cacld for $C_{12}H_{17}O_2Br$: C, 52.76; H, 6.27; Br, 29.25. Found: C, 52.75; H, 6.16; Br, 29.05. $[\alpha]_D$ = −18.83° ($CHCl_3$, $c$ = 1.03).

**(−)-(*E*)-(1*S*,6*R*)-8,8-Dimethyl-3-formyl-4-propylidene-7,9-dioxabicyclo[4.3.0]non-2-ene (49b).** *n*-BuLi (2.5 M in hexanes, 0.23 mL, 0.57 mmol), bromide **48b** (120 mg, 0.44 mmol) in THF (6 mL), and DMF (0.13 g, 1.76 mmol) were treated as per compound **22**. The product was purified by flash column chromatography eluting with hexanes–ethyl acetate (4:1) to give **49b** as a colorless oil (72 mg, 74%). $^1$H NMR ($CDCl_3$): $\delta$ 9.52 (s, 1H), 6.59 (t, 1H, $J$ = 7.3 Hz), 6.28 (d, 1H, $J$ = 3.4 Hz), 4.68 (dd, 1H, $J$ = 5.5, 3.3 Hz), 4.37 (q, 1H, $J$ = 4.8 Hz), 2.71 (dd, 1H, $J$ = 15.4, 5.3 Hz), 2.44 (dm, 1H, $J$ = 15.4 Hz), 2.20–2.06 (m, 2H), 1.32 (s, 3H), 1.29 (s, 3H), 0.97 (t, 3H, $J$ = 7.4 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 193.0 (d), 143.5 (d), 138.2 (s), 136.1 (d), 123.4 (s), 109.4 (s), 72.7 (d), 71.7 (d), 28.1 (t), 27.9 (q), 26.2 (q), 21.4 (t), 13.8 (q). IR ($CHCl_3$, cm$^{-1}$): 2735 (w), 1705 (s), 1645 (w). MS (*m/z*, rel intensity): 222 ($M^+$, 5), 164 (100), 147 (78). Exact mass calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1257. $[\alpha]_D$ = +55.61° ($CHCl_3$, $c$ = 1.30).

**(±)-(4*S*,6*S*,7*R*)- and (±)-(4*R*,6*R*,7*R*)-10-Propylidene-4-ethoxy-7-methyl-3-oxabicyclo[4.4.0]dec-1-ene (50a and 51a).** The aldehyde **49a** (75 mg, 0.46 mmol) and tris(6,6,7,7,-8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (73 mg, 0.07 mmol) were dissolved in ethyl vinyl ether (2 mL). The solution was stirred for 7.5 days at rt. The excess ethyl vinyl ether was removed under reduced pressure, and the residue was purified by flash column chromatography eluting with hexanes–ethyl acetate (40:1) to yield an inseparable 3.5:1 mixture of **50a** and **51a** as a colorless oil 94 mg (87%). **Major Isomer 50a.** $^1$H NMR ($CDCl_3$): $\delta$ 6.30 (d, 1H, $J$ = 1.9 Hz), 5.23 (dt, 1H, $J$ = 7.2, 2.2 Hz), 4.76 (dd, 1H, $J$ = 9.8, 1.8 Hz), 3.92 (dq, 1H, $J$ = 9.5, 7.1 Hz), 3.54 (dq, 1H, $J$ = 9.5, 7.1 Hz), 2.57–2.51 (m, 1H), 2.18 (ddd, 1H, $J$ = 13.3, 6.3, 1.8 Hz), 2.09–1.77 (m, 4H), 1.75–1.67 (m, 2H), 1.40 (ddd, 1H, $J$ = 12.8, 11.2, 9.8 Hz), 1.22 (t, 3H, $J$ = 7.1 Hz), 1.16–1.07 (m, 1H), 0.93 (t, 3H, $J$ = 7.5 Hz), 0.92 (d, 3H, $J$ = 6.4 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 135.0 (s), 134.9 (d), 123.4 (d), 119.3 (s), 100.0 (d), 64.4 (t), 40.5 (d), 38.7 (d), 34.7 (t), 34.3 (t), 27.6 (t), 20.8 (t), 19.8 (q), 15.2 (q), 14.5 (q). IR ($CHCl_3$, cm$^{-1}$): 1640 (s), 1625 (s). MS (*m/z*, rel intensity): 236 ($M^+$, 100), 191 (35), 149 (24). Exact mass calcd for $C_{15}H_{24}O_2$ 236.1777, found 236.1767. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.18; H, 10.21. **Minor Isomer 51a.** $^{13}$C NMR: $\delta$ 136.4 (d), 133.2 (s), 123.3 (d), 117.1 (s), 100.2 (d), 64.4 (t), 37.6 (d), 32.8 (t), 32.4 (t), 30.6 (d), 21.6 (t), 20.8 (t), 15.2 (q), 14.5 (q), 12.8 (q).

**(+)-(4*R*,5*R*,7*S*,11*S*)-9,9-Dimethyl-4-ethoxy-13-propylidene-3,8,10-trioxatricyclo[4.7.0.0$^{7,11}$]tridec-1-ene (50b).** The aldehyde **49b** (51 mg, 0.23 mmol) and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (36 mg, 0.03 mmol) were dissolved in ethyl vinyl ether (2 mL). The solution was stirred for 7 days at rt. Then, saturated aqueous sodium chloride (2 mL) was added to the solution, which was stirred for 2 h. The aqueous layer was extracted with diethyl ether (2 × 5 mL), and the combined organic layers were dried with anhydrous magnesium sulfate. The solvent was removed in vacuo. The product was then purified by flash column chromatography eluting with hexanes–ethyl acetate (6:1) to give 45 mg of pure **50b** as an oil (66%) and 8.6 mg (12%) of an inseparable 1.5:1 mixture of two compounds which could not be identified (one of them may be **51b**). $^1$H NMR ($CDCl_3$): $\delta$ 6.63 (d, 1H, $J$ = 2.1 Hz), 5.53 (dt, 1H, $J$ = 7.5, 1.1 Hz), 4.91 (dd, 1H, $J$ = 7.9, 2.4 Hz), 4.15 (dt, 1H, $J$ = 9.1, 6.6 Hz), 3.91 (dd, 1H, $J$ = 9.1, 7.1 Hz), 3.85 (dq, 1H, $J$ = 9.5, 7.1 Hz), 3.54 (dq, 1H, $J$ = 9.5, 7.1 Hz), 2.85 (ddd, 1H, $J$ = 14.3, 6.6, 1.0 Hz), 2.51–2.43 (m, 1H), 2.25 (ddd, 1H, $J$ = 13.5, 6.7, 2.4 Hz), 2.23–2.16 (m, 1H), 2.04 (dqi, 2H, $J$ = 7.5, 1.0 Hz), 1.73 (dt, 1H, $J$ = 13.5, 7.9 Hz), 1.45 (s, 3H), 1.31 (s, 3H), 1.20 (t, 3H, $J$ = 7.1 Hz), 0.94 (t, 3H, $J$ = 7.5 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 135.9 (d), 128.5 (s), 122.1 (d), 112.7 (s), 108.5 (s), 98.6 (d), 79.1 (d), 73.9 (d), 64.3 (t), 34.6 (q), 31.9 (t), 29.5 (t), 27.6 (q), 24.9 (q), 21.1 (t), 15.2 (q), 14.5 (q). IR ($CHCl_3$, cm$^{-1}$): 1625 (s), 1160 (s), 1125 (s), 1060 (s). MS (*m/z*, rel intensity): 294 ($M^+$, 100), 173 (33), 164 (53), 147 (41), 145 (34). Exact mass calcd for $C_{17}H_{26}O_4$ 294.1832, found 294.1822. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.68; H, 8.95. $[\alpha]_D$ = +0.34° ($CHCl_3$, $c$ = 1.17).

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**Supplementary Material Available:** $^1$H NMR and $^{13}$C NMR spectra of **25** and **42b** at 21 °C and −30 °C, COSY spectra of **25**, **33a**, **38**, **39**, **40**, **42–c**, and **50b**, NOESY spectra of **33a**, **42a**, **42c**, and **50b**, $^1$H–$^{13}$C CORRELATED spectra of **33a**, **40**, **42a–c**, and **50b**, and ORTEPs of **33a**, **42c**, and **53** (26 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.