Pergamon

Tetrahedron Vol. 51, No. 12, pp. 3455-3482, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00095-X

FACILE ACCESS TO THE ABC RING SYSTEM OF THE TAXANE DITERPENES VIA ANIONIC OXY-COPE REARRANGEMENTS

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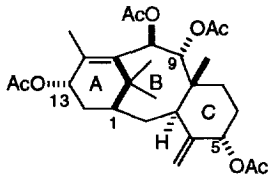
Abstract. The anionic oxy-Cope rearrangement of bicyclo[2.2.2]octadienols serves as a key step for the construction of substituted bicyclo[5.3.1]undecenones and provides a novel entry to the AB ring system of the taxane diterpenes. The bicyclo[2.2.2]octadienols **11a-e** underwent facile anionically-accelerated [3,3]-sigmatropic rearrangements to give bicyclo[5.3.1]undecenones **14a-e.** Such reorganizations were also found to proceed in more highly substituted systems as evidenced by the transformations **27a-c→28a-c**, **30→32**, and **31→33**. These bicyclo[5.3.1]undecenones were further functionalized by introducing a double bond conjugated to the carbonyl group (**27a→40**); moreover, oxygen functionality at C(13) could be introduced by allylic oxidation (**28a→41** and **40→42**). The enolates produced *in situ* by the anionic oxy-Cope rearrangement could be trapped by alkylating agents. These alkylations were highly stereoselective when the ketone enolate was trisubstituted as exemplified by the reactions **44→47** and **45→48**. This entry to the taxane diterpenes allows access to the tricyclic ABC framework of the taxanes by annelation of the C ring onto an AB ring subunit as illustrated by the sequence **30→49→50**.

The taxane diterpenes comprise a small but important group of novel and structurally complex natural products that are found in the leaves, roots, and stems of the English and Japanese yews (*Taxus baccata L., Taxus brevifolia Nutt., Taxus wallichiana Zucc.* and *Taxus cuspidata*), and new members of this unusual class of terpenes continue to be isolated.[1] The intense interest in this family of diterpenes, of which one of the simplest members is taxusin (**1**), has been stimulated by the observations that taxol (**2**),[2] cephalomannine,[3] taxotere® (**3**)[4] and other semi-synthetic derivatives[5] exhibit highly promising antitumor and antileukemic activity. Indeed, taxol (**2**) and taxotere® (**3**), which are presently undergoing clinical trials as drug candidates for treating several forms of cancer, appear to be especially promising against advanced human ovarian tumors. The mechanism of action of taxol appears to be unique among anticancer drugs since it promotes the formation of stable microtubules from tubulin, and by binding to microtubules,



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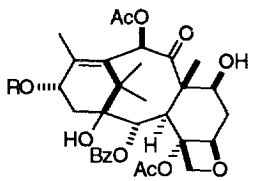
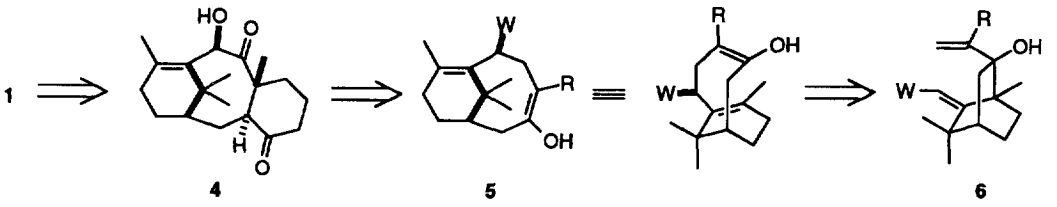


2: R = COCH(OH)CHPhNHCOPh
3: R = COCH(OH)CHPhNHBoc

it prevents disaggregation.[6] By contrast, other anticancer agents inhibit microtubule formation. The major obstacle to the practical and extensive use of taxol for cancer chemotherapy lies in its extraordinarily limited availability. It is presently isolated in only .0023% yield from the bark of the slow-growing Pacific yew (*Taxus brevifolia*), which is found in the old-growth forests of the Pacific northwest. However, it has recently become feasible to prepare taxol by semi-synthesis from the more readily available 10-deacetylbaccatin III,[7] which may be easily isolated from yew leaves. The exciting anticancer activity exhibited by taxol coupled with its low availability and complex structure has stimulated numerous innovative synthetic investigations[8] culminating first in the total synthesis of the unnatural enantiomer of taxusin (**1**)[9] and then recently in two landmark syntheses of taxol itself by Nicolaou[10] and Holton.[11]

Some years ago, we were attracted by the considerable challenge of designing a concise approach to the taxane diterpenes, the essential elements of which are outlined for the synthesis of taxusin (**1**) in retrosynthetic format in Scheme 1. The construction of the skeleton was envisaged to proceed in two distinct stages. In the first, a substituted bicyclo[2.2.2]octane **6** would be prepared as a substrate for an anionic oxy-Cope rearrangement[12] to generate the bicyclo[5.3.1]undec-7-ene ring system that constitutes the AB ring subunit of these formidable targets. Presumably the enolate **5** formed by this reorganization would then serve as an intermediate that could be elaborated into **4** by annelation of the C ring in the second phase of skeletal construction. Refunctionalization of **4** into taxusin might then be envisioned. The extension of this plan, should it ultimately prove successful, to the total synthesis of the significantly more demanding objective of taxol would require a more highly functionalized derivative of the bicyclo[2.2.2]octane **6** coupled with a protocol for the annelation of the C ring that would allow for the incorporation of the hydroxyl group at C(7). A full account of some of our results directed toward the solution of problems posed by the formation of substituted bicyclo[5.3.1]undec-7-enes via anionic oxy-Cope rearrangements constitutes the substance of this report.[13]

Scheme 1



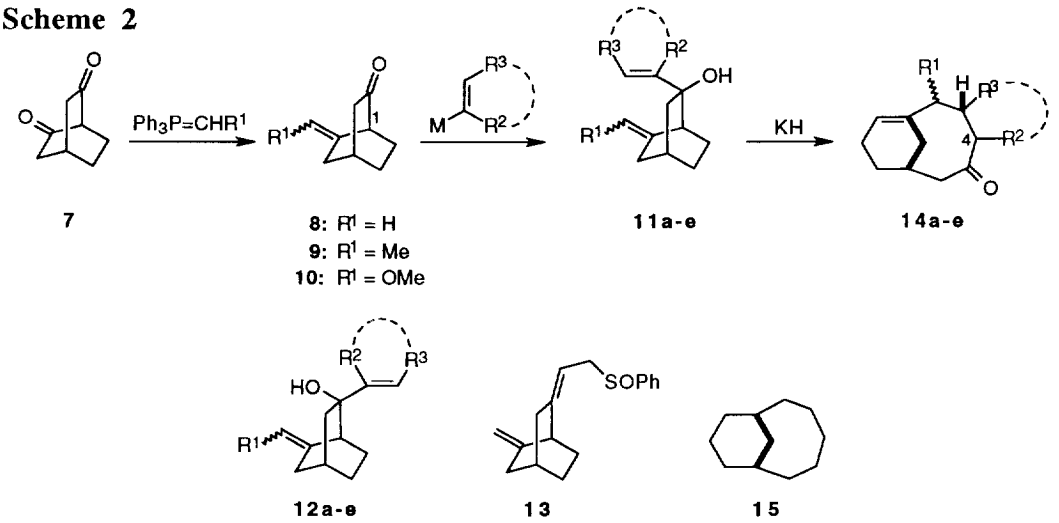
W = H, OR, SR

Preliminary Model Studies. The first question that needed to be resolved was whether bicyclo-[5.3.1]undec-7-enes could be prepared by the anionic oxy-Cope rearrangements of simple bicyclo[2.2.2]octadienols. Since there were no examples of such constructions at the outset of our investigations, we embarked upon a series of simple model studies to address this issue. Toward this end, we initially prepared the bicyclic dienols **11a-e** according to the reactions summarized in Scheme 2. Reaction of the dione **7**[14] with methylene triphenylphosphorane under salt-free conditions[15] afforded the bicyclic enone **8** in 79% yield. Similarly, reaction of **7** with ethylidene triphenylphosphorane afforded a mixture (*Z*/*E*= 15:1, 59% yield) of enones **9**. The stereochemistry about the olefinic bond was assigned as *Z* based upon a comparison of the ^{13}C NMR spectra of **8** and **9** in which all carbons except the bridgehead carbon at C(1) appear at approximately the same chemical shifts. The C(1) resonance for the *Z*-isomer of **9**

is 6.4 ppm upfield from the corresponding carbon in **8** owing to steric compression effects of C(1) with the olefinic methyl substituent. Treatment of **7** with methoxymethylene triphenylphosphorane gave **10** as an inseparable mixture (5:1, 51% yield) of geometric isomers. Although it was not possible to determine which of the two isomers was the major product by spectroscopic means, we assume that the Z-isomer dominated as observed in the case of **9**.

Subsequent addition of vinylmagnesium bromide to **8** gave a separable mixture (1.6:1; 81% yield) of epimeric dienols **11a** and **12a**. Several attempts to improve the yield of the desired **11a** by changing the reaction conditions or the organometallic reagent were unavailing. For example, the reactions of **8** with CH_2=CHLi, $(CH_2=CH)_3CuLi_2$, and $(CH_2=CH)_2CuCNLi_2$ furnished **12a** as the major product. We explored other means of improving the net stereochemical efficiency of this process, one of which involved a protocol for effecting the inversion of configuration of the stereochemistry of the tertiary alcohol function. In the event, reaction of the lithium alkoxide derived from **12a** with phenylsulfenyl chloride gave an intermediate allylic sulfenate ester that underwent [2,3]-sigmatropic rearrangement to give the allylic sulfoxide **13** as a mixture of diastereoisomers in 79% yield. When **13** was heated in methanol in the presence of trimethylphosphite or piperidine, an approximately 1:1 mixture of **11a** and **12a** was produced from a second [2,3]-sigmatropic rearrangement that proceeded equally across the stereochemically similar faces of the double bond. Greater diastereoselectivity in such processes may be observed in cases wherein the two faces of the double bond are more clearly differentiated.[16] The additions of other vinyl organometallic reagents to enones **8–10** similarly gave separable mixtures of the dienols **11b-e** and **12b-e** in 61–73% combined yields.

Scheme 2



7 **8**: R^1 = H; **9**: R^1 = Me; **10**: R^1 = OMe **11a-e** **14a-e**

12a-e **13** **15**

Series a: $R^1 = R^2 = R^3 = H$
b: $R^1 = R^3 = H$; R^2 = Me
c: R^1 = H; $R^2, R^3 = -(CH_2)_4-$
d: R^1 = Me; $R^2 = R^3 = H$
e: R^1 = OMe; $R^2 = R^3 = H$

With the requisite dienols **11a-e** in hand, the stage was set to test the viability of the key anionic oxy-Cope rearrangement, and the initial experiments were executed with the simplest member of this series **11a**. When **11a** was

deprotonated with potassium hydride in THF at room temperature, the anticipated [3,3]-sigmatropic rearrangement to deliver the bicyclo[5.3.1]undecenone **14a** in 82% yield was complete within 10 h. The rearrangement proceeded more readily in the presence of 18-crown-6 (1 equiv) or by employing hexamethylphosphoramide as a cosolvent, but the yields were slightly (5-10%) lower. The epimeric allylic alcohol **12a** did not suffer rearrangement when subjected to identical reaction conditions. Evidence supporting the structural assignment of **14a** was obtained by its conversion to the hydrocarbon **15**. Thus, catalytic hydrogenation of the bridgehead double bond of **14a** followed by removal of the ketone function by a two step procedure entailing Raney nickel desulfurization of the corresponding dithiolane ketal gave **15** in 58% overall yield from **14a**. The symmetry of **15** was apparent upon examination of its proton-decoupled ^{13}C NMR spectrum, which exhibited only seven lines.

In a similar fashion, each of the dienols **11b-e** was converted via anionic oxy-Cope rearrangement of its derived potassium alkoxide salt into the corresponding bicyclo[5.3.1]undecenones **14b-e**; the yield in each of these reactions was very good ranging from 75–86%. Moreover, with the exception of the methoxy substituted dienol **11e**, which required heating in refluxing glyme, all of these reorganizations occurred at room temperature. Compound **14b** was obtained as a mixture (1.5:1) of epimers at C(4). Although **14c** was isolated as a single compound, the relative stereochemistry at C(4) was not determined. It is noteworthy that the preparation of **14c** represented one of the first reports of the syntheses of the tricyclic carbon skeleton of the taxane ABC nucleus.

These initial successes verified that the anionic oxy-Cope rearrangements of the simple bicyclic dienols could be exploited for the facile construction of the bicyclo[5.3.1]undecenone ring system that constitutes the AB subunit of the taxane diterpenes. The next stage of the inquiry was designed to probe the scope and limitations of such processes and to ascertain whether such rearrangements might be exploited to access bicyclo[5.3.1]undecenones more highly endowed with the substitution patterns present in these natural targets.

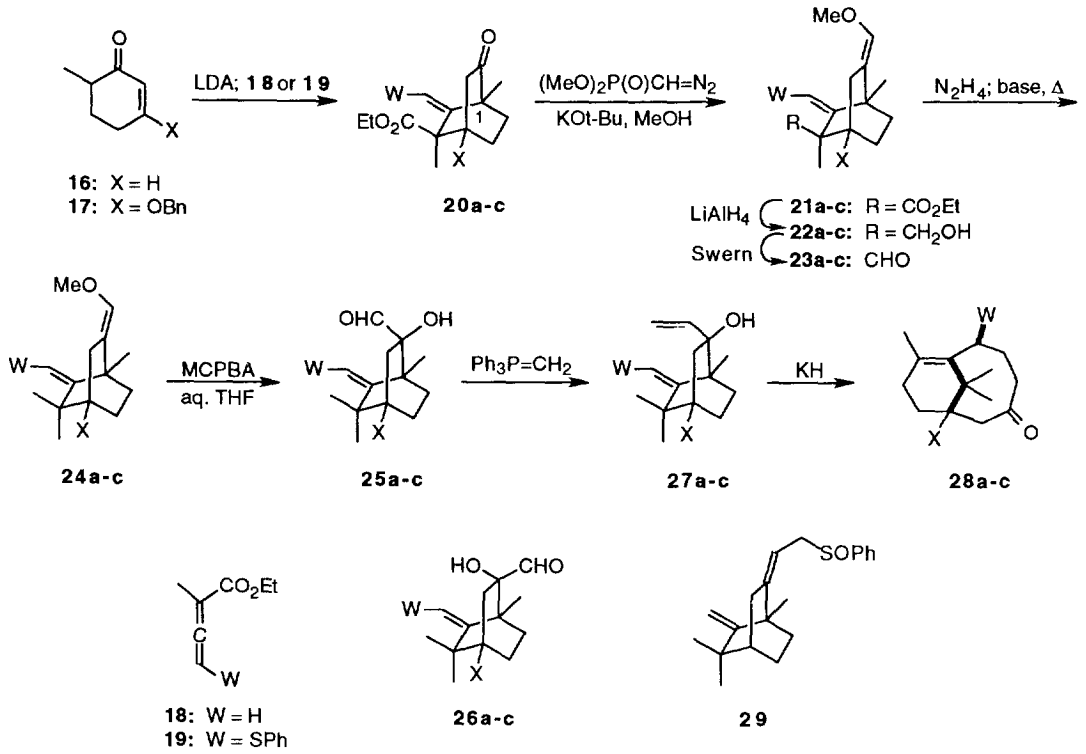
Preparation of the AB Ring System of Taxane Diterpenes. Comparison of the structure of **14a-e** with **4** reveals that additional methyl substitution is required. Furthermore, if an anionic oxy-Cope related to that depicted in Scheme 1 is to be applied to the synthesis of taxol, provision for an oxygen substituent at C(1) (taxol numbering) must be made. Although numerous avenues have been explored in our laboratories, the most useful entry to the suitably substituted bicyclo[2.2.2]octadienols **25a-c** is outlined in Scheme 3.

In our initial experiments, we exploited what has sometimes been termed as an enolate Diels-Alder reaction but which is mechanistically perhaps more accurately described as a double Michael reaction.[17] Toward this end, the kinetic dienolate derived from **16** was allowed to react with the known allene carboxylate **18**[18] to deliver the bicyclo[2.2.2]octane **20a** as the only isolable product in 60% yield. At the time this reaction was originally conducted, it represented the first example of a double Michael reaction involving an allene as the reaction partner, but Spitzner subsequently reported a closely related cycloaddition.[17b] The stereochemical outcome of this process, which is consistent with other published examples of double Michael reactions, was verified by X-ray analysis of the derived primary alcohol **22a** (*vide infra*).[19] Presumably bidentate coordination of the lithium counterion in the *endo*-transition state, which is not possible in the corresponding *exo*-transition state, is responsible for the enhanced *endo*-stereoselection observed in double Michael reactions relative to the corresponding Diels-Alder reactions.

It now remained to elaborate the bicyclic **20a** into the bicyclo[2.2.2]octadienol **27a** to test the viability of the key anionic oxy-Cope rearrangement. In preliminary experiments, we discovered that the sterically congested ketone function of **20a** was unreactive toward addition by a variety of vinyl organometallic reagents. After surveying a number of protocols to transform **20a** into **27a**, we eventually discovered one that could be reliably and efficiently

implemented. The sequence commenced with conversion of **20a** into the enol ether **21a** in 80% yield by treatment with diethyl diazomethylphosphonate in methanol in the presence of potassium *tert*-butoxide (*tert*-BuOK).[20] The ester function was then reduced to a methyl group by a straightforward sequence of reactions. Thus, reduction of **21a** with $LiAlH_4$ gave **22a** in 96% yield; subsequent Swern oxidation of **22a** followed by subjection of the intermediate aldehyde **23a** to the Huang-Minlon modification of the Wolff-Kishner reduction provided **24a** in 76% overall yield. Although several other methods to effect reduction of **22a** to **24a** via the derived tosylate, mesylate, iodide and phosphate were examined, none led to significant quantities of **24a**. When **24a** was oxidized with MCPBA in aqueous THF, a mixture (4:1, 94% yield) of **25a** together with its epimer **26a** was obtained; it was necessary to conduct this reaction in aqueous media to suppress the formation of mixed acetals. In preliminary experiments, we attempted to convert **26a** into **27a** according to the same tactics that were previously employed to effect the transformation **12a** → **13** → **11a**. Thus, Wittig olefination of **26a** followed by treatment of the alkoxide of the intermediate tertiary allylic alcohol with phenylsulfenyl chloride provided the allylic sulfoxide **29**; however, several attempts to induce a [2,3]-sigmatropic rearrangement of **29** to give the inverted allylic alcohol **27a** were unsuccessful and returned only unreacted starting material. The olefination of **25a** with methylene triphenylphosphorane proceeded

Scheme 3



without event to furnish **27a** in 87% yield. Deprotonation of **27a** with chemically purified KH[21] in the presence of 18-crown-6 at room temperature then delivered **28a** in 87% yield, thereby establishing the feasibility of the original strategy outlined in Scheme 1 for elaborating the methylated AB ring subunit of taxusin (**1**) via an anionic oxy-Cope rearrangement.

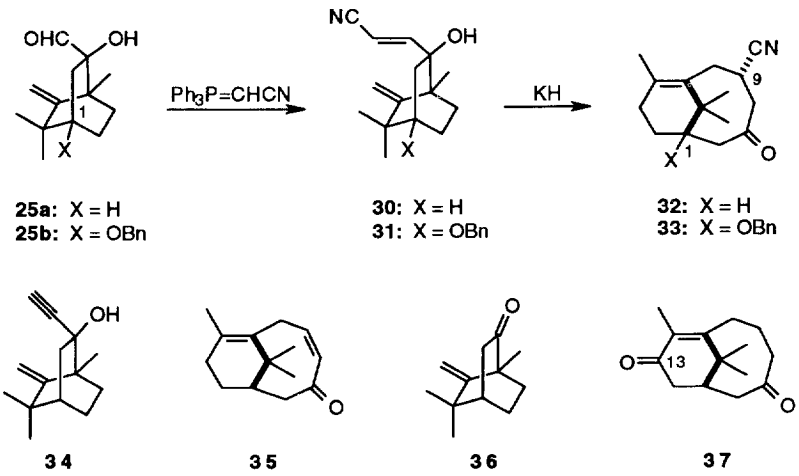
In the next phase of our investigations, we addressed some of the challenges associated with assembling more highly substituted AB ring systems such as those bearing functional groups at C(1) and C(10) (taxane numbering). The simplest approach to this problem would be to introduce the requisite functionality on the substrates employed in the double Michael reaction. Toward incorporating a hydroxyl substituent at C(1) of the taxane nucleus, the enolate of the vinylogous ester **17** was allowed to react with the allenic ester **18** via a double Michael reaction to provide **20b** as a single diastereoisomer in 95% yield (Scheme 3). Refunctionalization of **20b** to furnish the bicyclo[2.2.2]octadienol **27b** proceeded in 36% overall yield according to the six-step sequence of reactions previously established for the related conversion **20a** → **27a**. Although the experimental conditions were generally similar to those employed above, there were several slight modifications. For example, the best method for effecting the Wolff-Kishner reduction of **23b** to give **24b** (94% yield) entailed decomposing the intermediate hydrazone using *tert*-BuOK in toluene. Furthermore, the use of peroxy trichloroacetimidate as the oxidant for converting **24b** into the corresponding α-hydroxy aldehydes **25b** and **26b** gave a slightly more favorable mixture (6:1, 86% yield) of the desired epimer **25b**. Molecular reorganization of **27b** via anionic oxy-Cope rearrangement furnished **28b** in 87% yield.

We then examined the issue of preparing a bicyclo[5.3.1]undecenone bearing functionality at C(10) that might serve as a handle to introduce the oxygen functions at C(9) and C(10) of the taxanes. In one approach to this problem, a heteroatom-substituted buta-2,3-dienoate was considered as a possible reaction partner in the double Michael reaction. Unfortunately, allenes bearing such substitution were not known at the time, and it was necessary to devise a route to at least one such substance. Eventually we succeeded in preparing the modestly stable 4-phenylthiobuta-2,3-dienoate **19** in 70% yield according to the procedure utilized for making **18**. Although the double Michael reaction of **19** with the dienolate derived from **16** proceeded poorly, we discovered that **19** combined smoothly with the dienolate of **17** to afford the cycloadduct **20c** as a single stereoisomer in 78% yield. The six steps required to convert **20c** into **27c** according to prior art followed straightforwardly in 35% overall yield with the minor exception that oxidation of **24c** to the α-hydroxy aldehyde was most effectively achieved using *tert*-BuOOH/OsO_4 (cat.) in THF containing Et_4NOH. Careful control of the reaction conditions was necessary to minimize sulfoxide formation and oxidative cleavage of the double bond to give a ketone. The anionic oxy-Cope rearrangement of **27c** was less facile than either **27a** or **27b** and required brief heating at 50 °C in the presence of 18-crown-6 to furnish **28c** in 74% yield.

Having established protocols for introducing functionality at C(1) and C(10) of the taxane nucleus, it was now necessary to examine the rearrangements of dienols that would provide functionality at C(9). Since secondary nitriles may be oxidatively decyanated to ketones,[22] we reasoned that 9-cyano bicyclo[5.3.1]undecenones as **32** and **33** would be worthy targets. The electron withdrawing nitrile group would be expected to accelerate the rearrangement based upon theoretical considerations.[23] The α-hydroxy aldehydes **25a** and **25b** were thus converted by Wittig olefination into the unsaturated nitriles **30** and **31** in 93% and 83% yields, respectively. Upon treatment with KH, **30** and **31** underwent facile anionic oxy-Cope rearrangements to give the corresponding bicyclo[5.3.1]undecenones **32** and **33** in 90–95% yield (Scheme 4). If the rearrangement of **30** was allowed to proceed at room temperature, a mixture of nitriles epimeric at C(9) was obtained, whereas only **32** was isolated when the reaction was conducted at 0 °C. As another possible entry to bicyclo[5.3.1]undecenones functionalized at C(9), we attempted to induce the anionic

oxy-Cope rearrangement of the enynol **34**,[24] which was prepared in 79% yield by reaction of **25a** with diethyl diazomethylphosphonate.[20] However, under all of the conditions surveyed, none of the desired enone **35** was detected, and **36** was the only ketonic product isolated.

Scheme 4



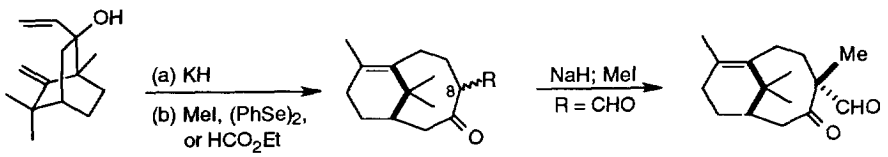
The taxane diterpenes possess an oxygen substituent at C(13) (taxane numbering), and a method for effecting the allylic oxidation of selected bicyclo[5.3.1]undecenones was developed. Although this issue was not examined in detail, we established that chromium trioxide/3,5-dimethylpyrazole[25] smoothly induced the oxidation of **28a** to furnish the dione **37** in 91% yield.

The experiments described thus far clearly demonstrated the efficacy of utilizing anionic oxy-Cope rearrangements of readily available dienols for the preparation of bicyclo[5.3.1]undecenones that bear functionality at C(1), C(9), C(10) and C(13) of the taxane AB ring nucleus. The basic strategy for the synthesis of the taxane diterpenes that is outlined in Scheme 1 appeared to be viable, but considerable work remained. The next task involved developing a workable plan to elaborate the C ring onto the AB ring subunit. Since the initial products of the anionic oxy-Cope rearrangements of **27a-c** are enolates, it occurred to us that these enolates might be trapped directly with suitable electrophiles to enable annelation of the C ring. Two issues would have to be addressed: (1) Is it possible to trap the enolates *in situ* with alkylating agents and other electrophiles? and (2) What is the stereochemistry of the alkylation of these intermediate enolates?

Elaboration of Bicyclo[5.3.1]undec-4-en-3-ones to a Taxane ABC Ring Subunit. Experiments were first executed to evaluate the feasibility of trapping the enolates formed *in situ* after the anionic oxy-Cope rearrangements of the bicyclo[2.2.2]octadienols. For example, when the enolate generated by treating **27a** with potassium hydride was quenched with methyl iodide, a mixture (ca. 2:1, 60% yield) of methyl ketones **38a,b** was produced (Scheme 5). It was not possible to establish the stereochemistry at C(8) of the major product. Introduction of a double bond at C(8) (taxane numbering) of the bicyclo[5.3.1]undecene nucleus was achieved by reaction of **27a** with potassium hydride followed by trapping the enolate with diphenyldiselenide to give a mixture (ca 15:85, 89%, yield) of epimeric phenylselenides **39a,b**; subsequent oxidation and elimination delivered the enone **35** in 70% yield.

Although the intermediate enolate generated from rearrangement of **27a** could also be trapped with ethyl formate to give the formyl ketone **40**, the yield for this process was only about 30%. On the other hand, formylation of **28a** with a ten-fold excess of $NaOMe/HCO_2Et$ in benzene gave **40** in 76% yield. Subsequent reaction of **40** with NaH followed by methylation of the intermediate enolate and non-aqueous work-up gave **41**, the structure of which was established by X-ray crystallographic analysis,[26] as the exclusive product (87% yield). It is interesting to note that the stereochemical course of this reaction is opposite to that observed by Holton in the alkylation of related bicyclo[5.3.1]undecanones.[27] Compound **41** underwent facile deformylation on exposure to water to give **38a,b** as a mixture of epimers at C(8).

Scheme 5



27a **38a,b**: R = Me; **39a,b**: R = SePh; **40**: R = CHO **41**

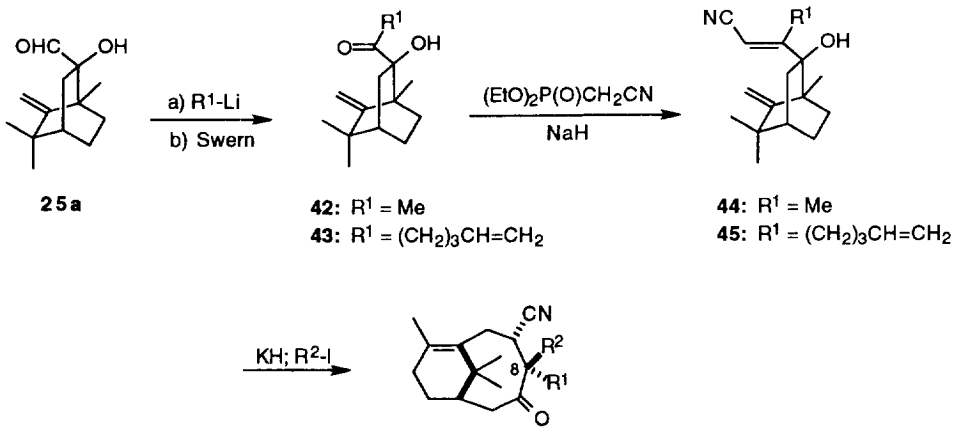
The application of an anionic oxy-Cope rearrangement to the preparation of intermediates that might be converted into taxane diterpenes demanded that elaboration of the quaternary stereocenter at C(4) be stereoselective. The experiments summarized in Scheme 5 establish that bicyclo[5.3.1]undecenolates produced by anionic oxy-Cope rearrangements of simple bicyclo[2.2.2]octadienols may be trapped by electrophiles. However, mixtures of epimeric products were obtained, and it was not possible to ascertain whether alkylation of the enolate was non-stereoselective or whether equilibration at C(8) occurred under the reaction conditions subsequent to alkylation. That methylation of the enolate of **40** furnished a single product, suggested that equilibration might be the problem, but conformational factors could also be involved. It was therefore necessary to examine the stereoselectivity of the alkylation of enolates that would be obtained upon rearrangement of more highly substituted substrates.

In the context of preparing intermediates that might be used in the synthesis of taxusin (**1**), the presence of a functional group at C(9) or C(10) that would allow eventual introduction of the requisite oxygen functionality was desirable. Toward this objective, compounds containing a cyano group at C(9) appeared especially attractive. Thus, the α-hydroxy aldehyde **25a** was transformed into the ketone **42** in 85% yield by sequential addition of methyllithium followed by Swern oxidation. Olefination of **42** via a Horner-Emmons reaction then provided **44** (81% yield) as the only geometric isomer. When **44** was treated with KH and the intermediate enolate protonated with water, a single product was formed in 90% yield to which the structure **46** has been tentatively assigned; the stereochemistry at C(8) was not definitely established. On the other hand, alkylation of the bicyclo[5.3.1]undecenolate generated *in situ* by the anionic oxy-Cope rearrangement of **44** with either 4-iodobutyl acetate or 5-bromopentene gave the corresponding products **47** (92% yield) and **48** (84% yield) as single stereoisomers. The structure of **47** was unequivocally established by X-ray analysis,[28] whereas the structure of **48** was assigned based upon analogy and comparison of its NMR spectra with that of **47**. Both **47** and **48** possesses the wrong stereochemistry at C(8) (taxane numbering), and thus cannot serve as intermediates in the synthesis of any of the taxane diterpenes.

Thus, although the alkylation of the bicyclo[5.3.1]undecenolate derived from **44** was highly stereoselective, the electrophile approached from the undesired *re* face. This observation suggested that the correct stereochemistry at C(8) could be established simply by reversing the order of introduction of the alkyl residues. Accordingly, **25a** was converted into **43** (83% yield) and then into the dienol **45** (94% yield based upon recovered starting material) by a straightforward modification of the sequence used to prepare **44**. Deprotonation of **45** with KH followed by reaction of the enolate with methyl iodide gave **49** as the sole product (88% yield); this structural assignment was confirmed by X-ray analysis.[28]

These results demonstrate that the alkylation of the enolates generated *in situ* by the anionic oxy-Cope rearrangements of **44** and **45** undergo highly stereoselective alkylation from the *re* face to give **47–49**. Whether the stereochemical course of these alkylations is dictated by the conformational bias inherent in the substituted bicyclic array or is the consequence of 1,2-induction directed by the adjacent nitrile function cannot be presently ascertained. Indeed, predicting the preferred conformation of substituted bicyclo[5.3.1]undecenolates may be problematic as is illustrated by the fact that Holton has observed alkylations of related bicyclo[5.3.1]undecenolates that occur in the opposite stereochemical sense.[27]

Scheme 6



25a

42: R^1 = Me
43: R^1 = $(CH_2)_3CH{=}CH_2$

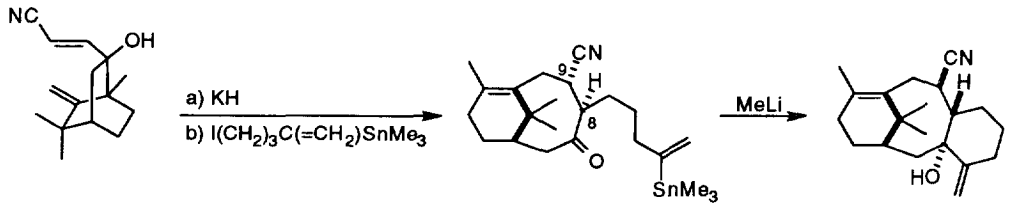
44: R^1 = Me
45: R^1 = $(CH_2)_3CH{=}CH_2$

46: R^1 = Me; R^2 = H
47: R^1 = Me; R^2 = $(CH_2)_4OAc$
48: R^1 = Me; R^2 = $(CH_2)_3CH{=}CH_2$
49: R^1 = $(CH_2)_3CH{=}CH_2$; R^2 = Me

The next challenge to be addressed in this quest to synthesize a naturally-occurring taxane diterpene was the formation of the tricyclic ring system by annelation of a functionalized C ring. After considering a number of possible tactics, we developed an approach that features the selective intramolecular addition of a vinyllithium reagent, which would be generated *in situ* from a vinylstannane (Scheme 7). The plan was based upon a number of previous observations indicating that the carbonyl groups in a number of bicyclo[5.3.1]undecenones were resistant to bimolecular nucleophilic attack, and α-substituted analogues were found particularly inert toward such addition. In the event, alkylation of the enolate produced upon the anionic oxy-Cope rearrangement of **30** with 5-iodo-2-trimethylstannylpentene,[29] furnished a mixture (2:1, 76% yield) of two diastereoisomeric products. The

stereochemistry at C(8) and C(9) of the major product was *tentatively* assigned as being that depicted in **50** based upon analogy with related alkylations examined previously (*cf* Scheme 6); however, *its structure was not unambiguously determined.* Subsequent treatment of the major product **50** with excess methyllithium generated *in situ* a vinyllithium reagent that underwent spontaneous cyclization to give a mixture (4:1, 58% yield) of the tricyclic substance **51**, the structure of which was unequivocally assigned by X-ray analysis,[28] and a stereoisomer whose structure was not determined. Comparison of the stereochemistry at the stereogenic centers of **50** with those in **51** reveals a discrepancy in the relative stereochemistry at C(8) and C(9). Unfortunately, we are presently unable to determine whether a series of epimerizations have occurred during the conversion of **50** into **51**, whether the structure assigned to **50** is incorrect, or whether some combination of both of these possibilities are responsible for this observation.

Scheme 7



30 **50** **51**

During the course of these studies, we have established that the anionic oxy-Cope rearrangements of a variety of substituted bicyclo[2.2.2]octadienols can be exploited for the facile construction of the AB ring system of the taxane diterpenes. Bicyclo[5.3.1]undecenones bearing functional groups at C(1), C(9), C(10), and C(13) are readily available according to this strategy. The enolates that formed *in situ* by the anionic oxy-Cope rearrangement may be easily trapped with a variety of alkylating agents, and in some cases this alkylation proceeds with a high level of stereoselectivity. Finally, it has been possible to annelate a functionalized six-membered ring to give compounds possessing the tricyclic ABC skeleton of the taxanes. Whether the novel strategy outlined in Scheme 1 may ultimately be applied to the total synthesis of members of the taxane family of diterpenes must await further experimentation.

EXPERIMENTAL PROCEDURES

General. Unless otherwise noted, all starting materials were obtained from commercial suppliers and were used without further purification. All solvents were dried according to established procedures by distillation from an appropriate drying agent under an inert atmosphere. Methyl iodide, chlorotrimethylsilane (TMS-Cl), diisopropylamine, and triethylamine were distilled from pulverized calcium hydride under nitrogen prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that had been oven and/or flame dried. Percent yields are given for compounds that were ≥ 95% pure as judged by ^{1}H NMR. Flash chromatography was performed according to the method of Still[34] with silica gel 60 (230-400 mesh ASTM). Semi-preparative high performance liquid chromatography (HPLC) was carried out with two successive 7 mm x 60 cm Porasil A columns. Melting points are uncorrected. Infrared (IR) spectra were recorded either neat or as solutions in $CHCl_3$ as indicated and are reported in wavenumbers (cm^{-1}) referenced to the 1601.8 cm^{-1} absorption of a polystyrene film. ^{1}H and ^{13}C NMR spectra were obtained as solutions

in deuterochloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts are reported in parts per million (ppm, δ) downfield relative from internal standard tetramethylsilane (TMS). Coupling constants are reported in hertz (Hz) to an accuracy of ± 0.2 Hz. Spectral splitting patterns are designated as s, singlet; br, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and comp, complex multiplet.

6-Methylenebicyclo[2.2.2]octan-2-one (8). Potassium hydride (1.82 g of a 35% dispersion in mineral oil, 15.9 mmol) was suspended in THF (10 mL), and hexamethyldisilazane (2.55 g, 15.8 mmol) was added. After stirring for 0.5 h at room temperature, THF (40 mL) and (methyl)triphenylphosphonium bromide (6.2 g, 17.4 mmol) were added. After stirring 15 min, HMPA (10 mL) was added, and the mixture was cooled to -78 °C. Dione **7** (2.00 g, 14.5 mmol) in THF (10 mL) was added, and the reaction was allowed to warm to -20 °C over 1 h. After stirring between -20 and -25 °C for 2 h, the reaction was allowed to warm to room temperature for 2 h, whereupon the reaction was poured into 10% NH_4Cl (100 mL). The aqueous layer was extracted with hexanes (4 x 100 mL), and the organic layers were combined and dried ($MgSO_4$). After removal of the excess solvents under reduced pressure, the residue was purified by column chromatography on silica gel eluting with hexanes/EtOAc (9:1) to give **8** (1.56 g, 79%) as a colorless liquid: IR (film) 2940, 1740 cm^{-1}; ^1H NMR (90 MHz) δ 4.87 (br s, 1 H), 4.77 (br s, 1 H), 2.75 (t, J = 1 Hz, 1 H), 1.40-2.50 (comp, 9 H); ^{13}C NMR (20 MHz) δ 212.1, 143.4, 110.8, 54.4, 44.1, 34.3, 28.2, 24.6, 24.3; mass spectrum *m/z* 136.0890 ($C_9H_{13}O$ requires 136.0888).

2-Ethenyl-6-methylenebicyclo[2.2.2]octan-2-ols (11a, 12a). Vinylbromide (2.5 mL, 25 mmol) in THF (5 mL) was added to a suspension of magnesium turnings (660 mg, 27.5 mmol) in THF (20 mL) containing a small piece of iodine at such a rate as to maintain a steady reflux following the initiation of the reaction. The reaction was heated at reflux for 1 h and cooled to -45 °C. To the heterogeneous solution was added dropwise **8** (425 mg, 3.12 mmol) in THF (5 mL), and stirring was continued at -45 °C for 1 h and then at room temperature for 1 h. The excess Grignard reagent was quenched by dropwise addition of 10% NH_4Cl (75 mL), and the resulting aqueous mixture was extracted with Et_2O (3 x 75 mL). The organic layers were combined and dried ($MgSO_4$). Removal of the excess solvents under reduced pressure and purification of the residue by preparative HPLC using hexanes/EtOAc (10:1) as the eluent gave **11a** (255 mg, 50%) and **12a** (130 mg, 31%) as colorless liquids.

For **11a**: IR (film) 3420 cm^{-1}; ^1H NMR (90 MHz) δ 6.00 (dd, J = 17, 10 Hz, 1 H), 5.15 (dd, J = 17, 1.5 Hz, 1 H), 4.88 (dd, J = 10, 1.5 Hz, 1 H), 4.65-4.80 (comp, 2 H), 1.30-2.40 (comp, 10 H); ^{13}C NMR (20 MHz) δ 148.4, 146.3, 109.8, 108.8, 73.2, 47.7, 42.1, 34.0, 27.0, 24.4, 20.9; mass spectrum, *m/z* 164.1204 ($C_{11}H_{16}O$ requires 164.1201), 117 (base).

For **12a**: ^1H NMR (90 MHz) δ 5.96 (dd, 1 H , J = 17, 10 Hz), 5.23 (dd, 1 H , J = 17, 1.5 Hz), 5.02 (dd, J = 10, 1.5 Hz, 1 H), 4.75-4.90 (br s, 2 H), 1.20-2.50 (comp, 10 H); ^{13}C NMR (20 MHz) δ 147.6, 143.5, 112.7, 110.3, 72.6, 47.9, 41.5, 34.3, 27.0, 24.4, 22.0; mass spectrum, *m/z* 164.1198 ($C_{11}H_{16}O$ requires 164.1201), 116, 93, 90, 78, (base), 76, 54.

6-Methylene-2-(1-methylethenyl)bicyclo[2.2.2]octan-2-ols (11b, 12b). To a mixture of Mg turnings (256 mg, 10.4 mmol) in THF (20 mL) containing a piece of iodine was added 2-bromopropene (1.20 g, 10.0 mmol), and the reaction was heated at reflux for 1 h. After stirring at room temperature for 0.5 h, the reaction was cooled to -45 °C and **8** (270 mg, 1.98 mmol) in THF (2 mL) was added dropwise. After stirring at -45 °C for 0.5 h, the reaction was stirred at room temperature for 1 h and quenched with 10% NH_4Cl (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The organic layers were combined and dried

($MgSO_4$). Removal of the excess solvents gave a mixture that was separated by preparative HPLC using hexanes/EtOAc (10:1) to give **8** (61 mg, 22%), **11b** (99 mg, 28%) and **12b** (118 mg, 35%) as colorless liquids.

For **11b**: IR (film) 3420 cm^{-1}; ^1H NMR (90 MHz) δ 4.93 (s, 1 H), 4.70 (m, 3 H), 2.79 (s, 3 H), 1.30-2.50 (comp, 10 H); ^{13}C NMR (20 MHz) δ 149.9, 148.9, 111.0, 108.4, 75.4, 45.1, 40.0, 33.8, 24.7, 27.3, 21.5, 18.8; mass spectrum, *m/z* 178.1357 ($C_{12}H_{18}O$ requires 178.1358), 134, 108, 92, (base), 79.

For **12b**: IR (film) 3440 cm^{-1}; ^1H NMR (90 MHz) δ 4.80-5.05 (comp, 4 H), 2.20-2.45 (comp, 3 H), 1.8-2.20 (comp, 3 H), 1.80 (s, 3 H), 1.30-1.70 (comp, 4 H); ^{13}C NMR (20 MHz) δ 147.9, 147.8, 111.6, 110.7, 74.7, 44.9, 39.8, 34.5, 27.0, 24.1, 22.0, 18.9; mass spectrum, *m/z* 178.1363 ($C_{12}H_{18}O$ requires 178.1358), 160, 145, 117, 94 (base), 79.

2-(1-Cyclohexen-1-yl)-6-methylenebicyclo[2.2.2]octan-2-ols (11c, 12c). Lithium metal (331 mg of a 35% dispersion in paraffin, 14.3 mmol) was suspended in Et_2O (10 mL), and freshly distilled 1-chlorocyclohexene (835 mg, 7.16 mmol) was added dropwise. After stirring at room temperature for 12 h, the reaction was ultrasonicated for 0.5 h. The mixture was cooled to 0 °C, and **8** (136 mg, 1.0 mmol) in Et_2O (1 mL) was added dropwise. After stirring for 1 h at 0 °C, saturated NH_4Cl (25 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 25 mL). The organic layers were combined and dried ($MgSO_4$), and the excess solvents were evaporated under reduced pressure to give a residue that was separated by preparative HPLC using hexanes/EtOAc (9:1) to provide recovered starting material **8** (23 mg), **11c** (44 mg, 20%) as a white solid (mp 65-67 °C) and **12c** (90 mg, 41%) as a colorless liquid.

For **11c**: IR ($CHCl_3$) 3500 cm^{-1}; ^1H NMR (90 MHz) δ 5.57-5.77 (comp, 1 H), 4.57-4.77 (comp, 2 H), 1.20-2.45 (comp, 18 H); ^{13}C NMR (20 MHz) δ 149.2, 142.1, 121.5, 108.1, 75.4, 45.1, 39.7, 33.8, 27.4, 25.4, 24.9, 24.1, 23.3, 22.4, 21.6; mass spectrum, *m/z* 218.1677 ($C_{15}H_{22}O$ requires 218.1671), 125, 94 (base), 79.

For **12c**: IR (film) 3400 cm^{-1}; ^1H NMR (90 MHz) δ 5.57-5.77 (comp, 1 H), 4.72-4.95 (comp, 2 H), 1.20-2.45 (comp, 18 H); ^{13}C NMR (20 MHz) δ 148.2, 140.0, 122.1, 110.3, 74.8, 44.9, 39.5, 34.7, 27.1, 25.6, 24.2, 23.3, 22.4, 22.2; mass spectrum, *m/z* 218.1671 ($C_{15}H_{22}O$ requires 218.1671), 200, 125, 94 (base), 79.

Bicyclo[5.3.1]undec-7-en-3-one (14a). To a suspension of KH (95 mg of a 35% dispersion in mineral oil, 0.82 mmol) in THF (2 mL) at 0 °C was added **11a** (90 mg, 0.55 mmol) in THF (1 mL). After 15 min, the ice bath was removed, and the reaction was stirred at room temperature for 10 h. The reaction was quenched with 10% NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined and dried ($MgSO_4$). Removal of the excess solvents under reduced pressure followed by column chromatography of the residue on silica gel using hexanes/EtOAc (9:1) as the eluent gave **14a** (74 mg, 82%) as a waxy solid: mp 40-43 °C; IR (film) 3320, 1690 cm^{-1}; ^1H NMR (90 MHz) δ 5.27-5.47 (comp, 1 H), 1.50-2.77 (comp, 15 H); ^{13}C NMR (20 MHz) δ 214.4, 138.1, 127.5, 47.4, 44.8, 36.4, 33.3, 32.5, 24.2, 23.7, 21.6; mass spectrum, *m/z* 164.1198 ($C_{11}H_{16}O$ requires 164.1201), 92 (base), 79 (base).

4-Methylbicyclo[5.3.1]undec-7-en-3-one (14b). A solution of the potassium alkoxide salt of **11b** was generated as above in THF was stirred at room temperature for 12 h. Work up as before followed by column chromatography on silica gel using hexanes/EtOAc (9:1) as the eluent gave **14b** in 77% yield as an approximately 1.5:1 ratio of epimers. IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR (90 MHz) δ 5.27-5.47 (comp, 1 H), 1.40-2.77 (comp, 14 H), 1.03 (d, J = 1.0 Hz, 1.5 H), 0.95 (d, J = 1.0 Hz, 1.5 H); mass spectrum, *m/z* 178.1358 ($C_{12}H_{18}O$ requires 178.1358), 160, 145, 134, 131, 117, 108, 92 (base).

Tricyclo[9.3.1.0^{3,8}]pentadec-1(14)-en-9-one (14c). A solution of the potassium alkoxide salt of **11c** dissolved in 22% HMPA-THF was stirred at 0 °C for 0.5 h and then at room temperature for 3 h. Work up as before followed by column chromatography on silica gel using hexanes/EtOAc (9:1) as the eluent gave **14c** in 75% yield as a white solid; mp 86-89 °C; IR ($CHCl_3$) 1680 cm^{-1}; ^{1}H NMR (90 MHz) δ 5.20-5.40 (comp, 1 H), 1.00-3.00 (comp, 21 H); ^{13}C NMR (20 MHz) δ 213.2, 138.0, 127.8, 55.2, 46.3, 36.7, 34.2, 32.9, 32.7, 32.1, 26.1, 22.7, 21.3, 20.9, 20.0; mass spectrum, *m/z* 218.1671 ($C_{15}H_{22}O$ requires 218.1671), 174, 92 (base).

Bicyclo[5.3.1]undecan-3-one. A solution of **14a** (185 mg, 1.13 mmol) in EtOAc (3 mL) containing 5% Pd/C (35 mg) was stirred under hydrogen (1 atm) at room temperature for 12 h. Chromatography on a column of silica gel using hexanes/EtOAc (9:1) gave bicyclo[5.3.1]undecan-3-one (147 mg, 78%) as a colorless liquid; IR (film) 1700 cm^{-1}; ^{1}H NMR (90 MHz) δ 1.1-3.0 (comp, 18 H); ^{13}C NMR (20 MHz) δ 215.5, 47.9, 45.0, 31.1, 30.7, 30.3, 29.3, 22.0, 16.2; mass spectrum, *m/z* 166.1361 ($C_{11}H_{18}O$ requires 166.1358), 148, 108, 95, 81 (base).

Spiro{bicyclo[5.3.1]undecane-3-2'-1',3'-dithiolane}. Bicyclo[5.3.1]undecan-3-one from the previous experiment (147 mg, 0.88 mmol) was dissolved in freshly distilled boron trifluoride Et_2Oate (0.71 g, 5.07 mmol), and 1, 2-ethanedithiol (0.5 mL, 5.9 mmol) was added with stirring. After 5 min, the solution was diluted with Et_2O (20 mL) and washed successively with 2 M NaOH (10 mL) and water (10 mL). The organic layer was dried ($MgSO_4$), and the excess solvents were removed under reduced pressure to give a residue that was purified by column chromatography on silica gel eluting with hexanes/EtOAc (9:1) to give the dithiolane (214 mg, 100%); ^{1}H NMR (90 MHz) δ 3.05-3.45 (comp, 4 H), 2.50-2.90 (comp, 2 H), 1.15-2.50 (comp, 16 H); ^{13}C NMR δ 71.3, 50.3, 47.3, 40.3, 37.4, 31.6, 31.1, 30.9, 30.8, 29.7, 23.8, 16.2; mass spectrum, *m/z* 242.1170 ($C_{13}H_{22}S_2$ requires 242.1163), 214, 181, 150, 131, 118 (base).

Bicyclo[5.3.1]undecane (15). A mixture of the dithioketal from the previous experiment (214 mg, 0.88 mmol) in absolute EtOH (20 mL) containing Raney nickel (W-2) (excess) was heated under reflux for 12 h. Upon cooling, the reaction was filtered through Celite, and the Celite pad was washed with absolute EtOH (2 x 5 mL) and pentane (2 x 20 mL). The filtrate was diluted with pentane (75 mL) and washed with saturated brine (3 x 50 mL), and the organic layer was dried ($MgSO_4$). Careful evaporation of the excess solvents under reduced pressure (25 mm of Hg, 25 °C) gave **15** (99 mg, 74%) as a colorless liquid: ^{1}H NMR (90 MHz) δ 1.00-2.20 (comp, 20 H); ^{13}C NMR (20 MHz) δ 32.8, 31.7, 31.6, 31.3, 28.2, 25.5, 16.0; mass spectrum, *m/z* 152.1562 ($C_{11}H_{20}$ requires 152.1565), 109, 96, 81, 67, 55, 41 (base).

Ethyl 4-thiophenyl-2-methylbuta-2,3-dienoate (19). Thiophenyl acetyl chloride (1.5 g, 6.5 mmol) was added dropwise to a solution of 2-(ethyl propionate)triphenylphosphorane (4.7 g, 13.0 mmol) in THF (25 mL), and the mixture was stirred for 1 h. Hexane (40 mL) was added to the reaction mixture, and the solids were removed by vacuum filtration and washed with hexane (2 x 10 mL). The combined filtrates and washings were concentrated under reduced pressure to furnish a residue, which was extracted with hexane (2 x 25 mL). The combined extracts were then removed under reduced pressure to give **19** (1.1 g, ca. 70%). The allene could not be obtained in a pure state due to its instability and was used immediately in the subsequent experiment. IR ($CHCl_3$) ν 2420, 1700 cm^{-1}; ^{1}H NMR (90 MHz) δ 7.22 (comp, 5 H), 6.13 (q, J = 3.0 Hz, 1 H), 4.10 (q, J = 7.5 Hz, 2 H), 1.78 (d, J = 3.0 Hz, 3 H), 1.22 (t, J = 7.5 Hz, 3 H).

Ethyl 2,4-dimethyl-3-methylene-5-oxobicyclo[2.2.2]octane-2-carboxylate (20a). Methyllithium (135 mL of 2.2 M Et_2O solution, 0.30 mol) was added in one portion to a solution of trimethyl[2-methyl-1,5-cyclohexadien-1-yl)oxy]silane (53.6 g, 0.30 mol) in DME (1075 mL) at 0 °C, and the solution was stirred for 30 min,

whereupon freshly distilled ethyl 2,3-butadienoate (44.5 g, 0.35 mol) was added with vigorous stirring reaction in one portion. After 10 min the mixture was partitioned between saturated NH_4Cl (500 mL) and Et_2O (3 x 300 mL). The combined organics were washed with saturated brine (500 mL) and dried (Na_2SO_4). Removal of the solvents under reduced pressure furnished a residue that was purified by HPLC using hexanes/EtOAc (10:1) to give **20a** (42.5 g, 60%) as a pale amber oil. IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR (250 MHz) δ 5.15 (s, 1 H), 5.07 (s, 1 H), 4.07 (q, J = 7.1 Hz, 2 H), 2.43 (dt, J = 19.0, 2.9 Hz, 1 H), 2.32 (m, 1 H), 2.21 (dd, J = 19.0, 2.6 Hz, 1 H), 2.10-1.97 (comp, 2 H), 1.69-1.51 (m, 2 H), 1.51 (s, 3 H), 1.17 (t, 7.1 Hz, 3 H), 1.09 (s, 3H); ^{13}C NMR (20 MHz) δ 211.6, 175.1, 150.2, 111.8, 60.8, 50.5, 49.9, 42.3, 36.9, 31.5, 26.1, 21.2, 16.5, 13.8; mass spectrum, *m/z* 236.1419 ($C_{14}H_{20}O_3$ requires 236.1412), 208, 163, 135, 121 (base), 105, 88 (base).

Ethyl 1-*O*-benzyloxy-2,4-dimethyl-3-methylenebicyclo[2.2.2]octane-5-one-2-carboxylate (20b). To a solution of LDA [prepared from diisopropylamine (61.0 g, 84.5 mL, 0.6 mol) in anhydrous Et_2O (434 mL) and *n*-BuLi (2.7 N in hexanes, 0.55 mol) at -10 °C] at -78 °C was added dropwise (1 h) a solution of **17** (108.6 g, 0.50 mol) in Et_2O (250 mL). Stirring was continued for 10 min, whereupon the solution of dienolate was warmed to 0 °C, and **18** (72.8 g, 0.58 mol) was added in one portion. After stirring an additional 1.5 h, saturated NH_4Cl (800 mL) was added, and the aqueous layer was extracted with Et_2O (3 x 800 mL). The combined Et_2O extracts were washed with water (1 L), saturated NaCl (1 L) and dried ($MgSO_4$). The excess solvents were removed under reduced pressure to give **20b** as a bright yellow oil, which was purified by Kugelrohr distillation (oven temperature: 165-170 °C/0.2 mm) to provide 162.7 g (95%) of **20b**, which solidified to a yellow crystalline solid upon standing; mp 53.5-55.5 °C. IR ($CHCl_3$) ν 1720 cm^{-1}; ^1H NMR (360 MHz) δ 7.20-7.35 (comp, 5 H), 5.02 (s, 1 H), 4.89 (s, 1 H), 4.49 (d, J = 11.7 Hz, 1 H), 4.05-4.20 (m, 2 H), 3.32 (dd, J = 18.4, 3.6 Hz, 1 H), 2.62 (d, J = 18.4 Hz, 1 H), 1.62-2.15 (comp, 5 H), 1.63 (s, 3 H), 1.18 (t, J = 7.1 Hz, 3 H), 1.15 (s, 3 H); ^{13}C NMR (90 MHz) δ 207.9, 173.7, 151.7, 138.9, 128.1, 127.1, 126.6, 110.0, 77.5, 64.2, 60.8, 55.1, 50.6, 45.2, 29.6, 26.8, 22.2, 16.1, 13.8; mass spectrum *m/z* 342.1818 ($C_{21}H_{26}O_4$ requires 342.1831), 327, 296, 269, 193, 177, 163, 107, 91 (base). Anal Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65; Found: C, 73.61; H, 7.75.

Ethyl 1-*O*-Benzyloxy-2,4-dimethyl-3-thiophenylmethylenebicyclo[2.2.2]octane-5-one-2-carboxylate (20c). A solution of **17** (7.4 g, 34.5 mmol) in Et_2O (25 mL) was added dropwise with stirring to a solution of LDA [prepared from *i*-Pr_2NH (5.05 mL, 36.0 mmol) and *n*-BuLi (11.2 mL, 3.0 N in hexane) in Et_2O (300 mL) at 0 °C] at -78 °C, and the resulting solution was stirred for 1 h at -78 °C and then allowed to warm slowly (1 h) to 0 °C. A solution of crude allenic ester **19** (14.0 g, ca. 60 mmol) dissolved in Et_2O (200 mL) was added and the resulting solution stirred for 2.5 h at 0 °C. The reaction was quenched by the addition of saturated NH_4Cl (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 200 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure to provide a residue that was purified by HPLC using EtOAc/hexanes (1:8) as the eluent to afford **20c** (12.0 g, 78%); as colorless crystals, mp 78-79 °C [hexanes/EtOAc (10/1)]. IR ν 1730 cm^{-1}; ^1H NMR (300 MHz) δ 7.18-7.35 (comp, 10 H), 6.11 (s, 1H), 4.53 (center of AB quartet, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 17.9 Hz, δ_A = 4.56, δ_B = 4.50, 2 H), 4.00-4.25 (m, 2 H), 3.22 (dd, J = 18.5 Hz, J = 3.6 Hz, 1 H), 2.63 (d, J = 18.5 Hz, 1 H), 1.59-2.20 (comp, 4 H), 1.75 (s, 3 H), 1.20 (s, 3 H), 1.18 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 207.2, 172.5, 143.4, 138.8, 135.8, 129.0, 128.2, 127.1, 126.7, 126.5, 120.2, 77.8, 64.1, 61.1, 54.3, 51.6, 44.5, 29.3, 26.3, 18.9, 16.8, 13.8; Anal. Calcd for $C_{27}H_{30}O_4S$: C, 71.97; H, 6.71; S, 7.12; Found: C, 71.79; H, 6.67; S, 6.92.

Ethyl 2,4-dimethyl-3-methylene-5-(methoxymethylene)bicyclo[2.2.2]octane-2-carboxylate (21a). To a solution of diethyl (diazomethyl)phosphonate (DAMP) (50.0 g, 0.275 mol) and **20a** (13.0 g, 0.055 mol) in dry MeOH (90 mL) at 0 °C was added a solution of *tert*-BuOK (31.0 g, 0.275 mol) in dry MeOH (70 mL) while maintaining the reaction temperature below 20 °C. The reaction mixture was allowed to warm to room temperature, stirred 16 h and then poured into saturated $NaHCO_3$ (500 mL). The mixture was extracted with CH_2Cl_2 (5 x 100 mL), and the combined organic extracts were dried (Na_2SO_4). The excess solvents were removed under reduced pressure, and the residue was purified by preparative HPLC using hexanes/EtOAc (10:1) to give **21a** (11.5 g, 80%) as a colorless oil: IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR (250 MHz) δ 5.73 (t, *J* = 2.5 Hz, 1 H), 5.02 (s, 1 H), 4.84 (s, 1 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 3.52 (s, 3 H), 2.30 (dq, *J* = 17.5, 2.8 Hz, 1 H), 2.17 (dt, *J* = 17.5, 2.8 Hz, 1 H), 2.10 (m, 1 H), 1.85 (m, 1 H), 1.54-1.36 (m, 3 H), 1.41 (s, 3 H), 1.20 (t, *J* = 7.0 Hz, 3 H), 1.12 (s, 3 H); ^{13}C NMR (63 MHz) δ 176.0, 155.9, 139.1, 119.1, 107.0, 60.5, 59.3, 50.3, 37.5, 35.5, 35.0, 28.7, 26.5, 21.8, 20.4, 14.1; mass spectrum, *m/z* 264.1717 ($C_{16}H_{24}O_3$ requires 264.1725), 249, 232, 219, 191 (base), 159.

Ethyl 1-*O*-Benzyloxy-2,4-dimethyl-3-methylene-5-methoxymethylenebicyclo[2.2.2]octane-2-carboxylate (21b). Prepared from **20b** (38.4 g, 0.11 mol) according to the procedure described above to give 35.9 g (86%) of **21b** as a viscous yellow oil. IR ($CHCl_3$) ν 1725, 1685 cm^{-1}; ^1H NMR (360 MHz) δ 7.18-7.32 (comp, 5 H), 5.79 (t, *J* = 2.1 Hz, 1 H), 4.85 (s, 1 H), 4.62 (s, 1 H), 4.50 (d, *J* = 11.5 Hz, 1 H), 4.47 (d, *J* = 11.5 Hz, 1 H), 4.02-4.21 (comp, 2 H), 3.58 (s, 3 H), 3.10 (br d, *J* = 16.0 Hz, 1 H), 2.64 (dd, *J* = 16.0, 1.5 Hz, 1 H), 1.85-1.95 (m, 2 H), 1.59-1.67 (m, 2 H), 1.54 (s, 3 H), 1.18 (t, *J* = 7.2 Hz, 3 H), 1.15 (s, 3 H); ^{13}C NMR (90 MHz) δ 174.3, 158.0, 140.0, 138.7, 127.9, 126.7, 126.6, 119.4, 104.5, 77.8, 63.6, 60.4, 59.2, 55.2, 37.3, 34.6, 31.2, 27.5, 22.7, 19.7, 13.9; mass spectrum *m/z* 370.2151 ($C_{23}H_{30}O_4$ requires 370.2144), 355, 338, 279, 265, 205, 173, 145, 91 (base).

Ethyl 1-*O*-Benzyloxy-2,4-dimethyl-3-phenylthiomethylene-5-methoxymethylenebicyclo-[2.2.2]octane-2-carboxylate (21c). Prepared from **20c** (6.4 g, 14.3 mmol) according to the procedure described above to give **21c** (5.3 g, 78%); mp 98-99 °C (from EtOH). IR ν 1725 cm^{-1}; ^1H NMR (90 MHz): δ 7.10-7.30 (comp, 10 H), 5.89 (s, 1 H), 5.78 (t, *J* = 2 Hz, 1 H), 4.48 (s, 2 H), 3.80-4.30 (m, 2 H), 3.58 (s, 3 H), 2.93 (br d, *J* = 17 Hz, 1 H), 2.62 (dd, *J* = 17, 3 Hz, 1 H), 1.67 (s, 3H), 1.50-2.10 (comp, 4 H), 1.18 (s, 3 H), 1.16 (t, *J* = 7 Hz, 3 H); ^{13}C NMR (50 MHz) δ 172.9, 152.4, 139.8, 139.0, 137.3, 129.1, 128.9, 128.8, 128.1, 126.9, 126.6, 126.0, 118.9, 113.4, 78.0, 63.7, 60.7, 59.4, 54.6, 38.9, 34.7, 30.7, 27.3, 20.6, 19.3, 19.1, 14.0; Anal. Calcd. for $C_{29}H_{34}O_4S$: C, 72.77; H, 7.16; S, 6.69. Found: C, 72.98; H, 6.91; S, 6.83.

5-Hydroxymethyl-1,5-dimethyl-6-methylene-2-methoxymethylenebicyclo[2.2.2]octane (22a). A solution of **21a** (32.8 g, 0.12 mol) in THF (90 mL) was added dropwise to a suspension of $LiAlH_4$ (7.0 g, 0.19 mol) in THF (115 mL) at 0 °C. Upon completion of the addition, the mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was then cooled to 0 °C and quenched with stirring by dropwise addition of 6.5% aqueous THF (107 mL), aqueous 10% NaOH (7 mL), and water (21 mL). The resulting mixture was stirred for 1 h, and the white solids were removed by vacuum filtration and thoroughly washed with Et_2O. The filtrates were combined and concentrated under reduced pressure to give **22a** (26.4 g, 96%) as a white solid, mp 96-97 °C; ^1H NMR (250 MHz) δ 5.74 (t, *J* = 2.5 Hz, 1 H), 4.78 (s, 1 H), 4.61 (s, 1 H), 3.54 (s, 3 H), 3.48 (d, *J* = 11.0 Hz, 1 H), 3.29 (d, *J* = 11.0 Hz, 1 H), 2.56 (dq, *J* = 17.5, 3.2 Hz, 1 H), 2.09 (dt, 17.5, 2.5 Hz, 1 H), 1.40-1.91 (comp, 6 H), 1.20 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (63 MHz) δ 160.7, 138.7, 120.5, 102.6, 69.8, 59.2,

42.5, 37.5, 35.1, 32.5, 27.3, 23.9, 22.9, 20.3; mass spectrum, *m/z* 222.1618 ($C_{14}H_{22}O_2$ requires 222.1620), 207, 191 (base), 149, 105, 91. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.73; H, 9.95.

2-Methoxymethylene-4-*O*-benzyloxy-5-hydroxy-6-methylene-1,5-dimethylbicyclo[2.2.2]-octane (22b). Prepared from **21b** (35.9 g, 0.1 mol) according to the previous procedure except using Et_2O as the solvent to provide 31.5 g (99%) of **22b** as an opaque, colorless oil. IR ($CHCl_3$) ν 3500, 2920, 1690 cm^{-1}; ^1H NMR (360 MHz) δ 7.23-7.36 (comp, 5 H), 5.78 (t, *J* = 2.5 Hz, 1 H), 4.81 (s, 1 H), 4.68 (s, 1 H), 4.55 (d, *J* = 10.9 Hz, 1 H), 4.51 (d, *J* = 10.9 Hz, 1 H), 3.90 (d, *J* = 11.3 Hz, 1 H), 3.66 (br s, 1 H), 3.59 (s, 3 H), 3.27 (br d, *J* = 11.3 Hz, 1 H), 2.77 (dd, *J* = 16.6, 2.6 Hz, 1 H), 2.70 (ddd, *J* = 16.6, 2.6, 2.6 Hz, 1 H), 1.84-2.02 (comp, 2 H), 1.51-1.71 (comp, 2 H), 1.42 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (90 MHz) δ 159.2, 139.3, 138.6, 128.3, 127.3, 127.1, 118.7, 103.1, 80.6, 70.7, 63.6 59.3, 46.2, 36.9, 34.5, 30.6, 25.4, 20.5, 19.9; mass spectrum *m/z* 328.2032 ($C_{21}H_{28}O_3$ requires 328.2038), 328, 251, 237, 219, 91 (base).

2-Methoxymethylene-4-*O*-benzyloxy-5-hydroxymethyl-6-phenylthiomethylene-1,5-dimethylbicyclo[2.2.2]octane (22c). Prepared from **21c** (5.54 g, 11.6 mmol) according to the procedure described above except using Et_2O as a solvent to give crude **22c**, which was recrystallized from hexanes/EtOAc (ca. 8:1) to give 4.53 g (90%) of pure alcohol **22c**, mp 120-121 °C. IR ν 3430 cm^{-1}; ^1H NMR (90 MHz): δ 7.10-7.30 (comp, 10 H), 5.92 (s, 1 H), 5.76 (t, *J* = 2 Hz, 1 H), 4.53 (s, 2 H), 4.13 (d, *J* = 11 Hz, 1 H), 3.90 (d, *J* = 11 Hz, 1 H), 2.80 (m, 2 H), 1.60-2.10 (comp, 4 H), 1.67 (s, 3 H), 1.10 (s, 3 H); Anal. Calcd. for $C_{27}H_{32}O_3S$: C, 74.26; H, 7.40; S, 7.34. Found: C, 74.54; H, 7.65; S, 7.16.

2,4-Dimethyl-3-methylene-5-(methoxymethylene)bicyclo[2.2.2]octane-2-carbox-aldehyde (23a). To a solution of DMSO (1.36 g, 17.1 mmol) in CH_2Cl_2 (15 mL) cooled to -65 °C was added slowly dropwise trifluoroacetic anhydride (1.8 mL, 12.8 mmol) in CH_2Cl_2 (10 mL). After 15 min, **22a** (1.90 g, 8.55 mmol) in CH_2Cl_2 (10 mL) was added slowly dropwise. The temperature was maintained at -50 °C for 6 h, whereupon triethylamine (4.8 mL, 34.2 mmol) was added dropwise. After stirring for 15 min, the reaction mixture was allowed to warm to room temperature and poured into 10% NH_4Cl (75 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure, and the crude product was purified by preparative HPLC using hexanes/EtOAc (15:1) to give **23a** (1.46 g, 78%) as a colorless liquid. IR ($CHCl_3$) ν 1716 cm^{-1}; ^1H NMR (250 MHz) δ 9.51 (s, 1 H), 5.71 (dt, *J* = 0.6, 2.6 Hz, 1 H), 5.01 (s, 1 H), 4.64 (s, 1 H), 3.53 (s, 3 H), 2.47 (dq, *J* = 17.8, 3.2 Hz, 1 H), 2.18 (dt, *J* = 17.8, 2.7 Hz, 1 H), 1.97 (m, 1 H), 1.93-1.80 (m, 1 H), 1.40-1.58 (m, 3 H), 1.22 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (63 MHz) δ 204.5, 155.8, 139.5, 119.0, 106.3, 59.4, 53.6, 37.5, 34.0 (2 C's), 28.0, 22.7, 10.1; mass spectrum, *m/z* 220.1469 ($C_{14}H_{20}O_2$ requires 220.1463), 191.

1-*O*-Benzyloxy-2,4-dimethyl-3-methylene-5-methoxymethylenebicyclo[2.2.2]-octane-2-carboxaldehyde (23b). Prepared from **22b** (60.3 g, 0.18 mol) according to the procedure described above to afford 53.5 g (89%) of **23b** as a beige crystalline solid; mp 90.5-92 °C. IR ($CHCl_3$) ν 2940, 1720, 1680 cm^{-1}; ^1H NMR (360 MHz) δ 9.71 (s, 1 H), 7.31-7.45 (comp, 5 H), 5.83 (t, *J* = 2.4 Hz, 1 H), 4.97 (s, 1 H), 4.55 (s, 1 H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1 H), 3.60 (s, 3 H), 2.81 (d, *J* = 2.4 Hz, 2 H), 1.88-1.94 (comp, 2 H), 1.62-1.73 (comp, 2 H), 1.39 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR (90 MHz) δ 200.6, 153.9, 139.7, 139.2, 128.2, 127.1, 126.8, 118.1, 107.1, 78.0, 63.7, 59.5, 58.0, 37.3, 34.2, 30.7, 27.0, 19.7, 18.2; mass spectrum *m/z* 326.1895 ($C_{21}H_{26}O_3$ requires 326.1882), 294, 265, 235, 203, 175, 147, 133, 119, 105, 91 (base).

1-*O*-Benzyloxy-2,4-dimethyl-3-phenylthiomethylene-5-methoxymethylenebicyclo-[2.2.2]-octane-2-carboxaldehyde (23c). Prepared from **22c** (4.52 g, 10.4 mmol) according to the procedure described above to give pure **23c** (3.86 g, 86%); mp 102-103 °C (from EtOH). IR ν 1725 cm^{-1}; ^1H NMR (90 MHz): δ 9.72 (s, 1 H), 7.10-7.30 (comp, 10 H), 6.01 (s, 1 H), 5.80 (t, *J* = 2 Hz, 1 H), 4.43 (s, 2 H), 3.54 (s, 3 H), 2.68 (m, 2 H), 1.67 (s, 3 H), 1.50-2.10 (comp, 4 H), 1.17 (s, 3 H); Anal. Calcd. for $C_{27}H_{30}O_3S$: C, 74.61; H, 6.97; S, 7.38. Found: C, 74.81; H, 6.85; S, 7.65.

2-(Methoxymethylene)-6-methylene-1,5,5-trimethylbicyclo[2.2.2]octane (24a). A solution of **23a** (13.2 g, 60 mmol), anhydrous hydrazine (2.88 g, 90 mmol) in 2-hydroxyethyl Et_2O (35 mL) was stirred for 90 min at room temperature. Then KOH (7.5 g, 134 mmol) was added and the mixture was heated 2.5 h to 230 °C. After the reaction was cooled to room temperature and diluted into a 10% NH_4Cl (900 mL), the turbid mixture was extracted with CCl_4 (3 x 250 mL). The organic layers were combined, dried ($MgSO_4$) and carefully concentrated under reduced pressure to give **24a** (12.1 g, 98%) as a colorless liquid: ^1H NMR (250 MHz) δ 5.75 (dt, *J* = 0.5, 2.6 Hz, 1 H), 4.72 (s, 1 H), 4.65 (s, 1 H), 3.54 (s, 3 H), 2.56 (dq, *J* = 17.4, 3.2 Hz, 1 H), 2.10 (dt, *J* = 17.4, 2.6 Hz, 1H), 1.83-1.92\ (m, 1 H), 1.40-1.55 (comp, 3 H), 1.14 (s, 3 H), 1.08 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (63 MHz) δ 164.6, 138.6, 120.9, 101.3, 59.3, 38.1, 37.9, 37.5, 34.3, 30.1, 29.7, 27.9, 23.4, 20.6; mass spectrum, *m/z* 206.1675 ($C_{14}H_{22}O$ requires 206.1671), 191 (base), 177, 163, 149.

2-Methoxymethylene-4-*O*-benzyloxy-6-methylene-1,5,5-trimethylbicyclo[2.2.2]-octane (24b). A mixture of **23b** (53.5 g, 0.16 mol) and anhydrous hydrazine (81.1 g, 80.2 mL, 2.5 mol) was thoroughly purged with a stream of nitrogen and then heated at 100 °C for 3.5 h during which time the two phase mixture became homogeneous. After cooling to room temperature, the excess hydrazine was removed *in vacuo* (0.1 mm, dry ice trap), and the resulting opaque white oil was dissolved in anhydrous toluene (630 mL). To the rapidly stirred solution of hydrazone thus prepared was added in one portion *tert*-BuOK (24.0 g, 0.21 mol), and the suspension was heated at reflux for 2.5 h and then cooled to rt. The reaction was quenched by gradual addition of water (100 mL), the layers were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with saturated NaCl (800 mL) and dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography using hexanes/EtOAc (20:1) to afford 48.0 g (94%) of **24b** as a white waxy solid. IR ($CHCl_3$) ν 2900-3000, 1680 cm^{-1}; ^1H NMR (360 MHz) δ 7.21-7.38 (comp, 5 H), 5.76 (t, *J* = 2.5 Hz, 1 H), 4.73 (s, 2 H), 4.54 (d, *J* = 11.7 Hz, 1 H), 4.48 (d, *J* = 11.7 Hz, 1 H), 3.58 (s, 3 H), 2.62 (dd, *J* = 16.5, 2.5 Hz, 1 H), 2.52 (dt, *J* = 16.5, 2.5 Hz, 1 H), 1.78-1.96 (comp, 2 H), 1.52-1.68 (comp, 2 H), 1.23 (s, 3 H), 1.16 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (90 MHz) δ 164.0, 140.3, 138.8, 128.1, 126.7, 119.8, 101.4, 77.1, 63.4, 59.4, 42.9, 37.4, 35.0, 30.1, 25.9, 25.6, 25.5, 20.3. Mass spectrum *m/z* 312.2097 ($C_{21}H_{28}O_2$ requires 312.2089), 312, 221, 189, 161, 147, 91 (base).

2-Methoxymethylene-4-*O*-benzyloxy-6-phenylthiomethylene-1,5,5-trimethylbicyclo[2.2.2]-octane (24c). A mixture of **23c** (3.80 g, 8.8 mmol), KOH [2.91 g (85% by weight), 44.0 mmol], and anhydrous hydrazine (1.40 mL, 44.0 mmol) in diethylene glycol (25 mL) was heated at 125 °C for 20 min, 150 °C for 20 min and 205 °C for 4 h. After cooling to room temperature, water (50 mL) was added, and the aqueous mixture was extracted with Et_2O (4 x 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by HPLC eluting with 3.5% EtOAc/hexanes to afford **24c** (3.20 g, 84%) as a white solid; mp 100-101 °C (from hexanes/EtOAc); ^1H NMR (90 MHz) δ 7.10-7.40 (comp, 10 H), 5.82 (s, 1 H), 5.74 (t, *J* = 2 Hz, 1 H), 4.50 (comp, 2 H), 3.57 (s, 3 H), 2.58 (comp, 2 H), 1.40-2.00 (comp, 4 H), 1.49 (s, 3 H), 1.41 (s, 3 H), 1.09

(s, 3 H); ^{13}C NMR (50 MHz) δ 155.2, 139.2, 129.0, 128.6, 128.4, 128.2, 127.1, 126.9, 125.9, 119.5, 111.4, 96.2, 63.4, 59.4, 43.3, 39.3, 35.3, 30.0, 25.8, 21.3, 20.7, 20.4; Mass spectrum, *m/z* 420 (M^+), 329, 311, 219, 161, 145, 123, 105, 91 (base). Anal. Calcd. for $C_{27}H_{32}O_2S$: C, 77.09; H, 7.68; S, 7.62. Found: C, 77.26; H, 7.80; S, 7.73.

2-Hydroxy-6-methylene-1,5,5-trimethylbicyclo[2.2.2]octane-2-carboxaldehyde (25a). MCPBA (5.00 g of 85% technical grade, 24.8 mmol) was added in small portions (5 min) with stirring to a solution of **24a** (3.40 g, 16.6 mmol) in 33% aqueous THF (235 mL). After stirring for 10 min, the reaction was poured into a saturated solution of $Na_2S_2O_3$ (100 mL), and the resulting mixture was stirred for 15 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (150 mL) and dried ($MgSO_4$). Removal of the solvents under reduced pressure furnished a mixture that was separated by preparative HPLC using hexanes/EtOAc (15:1) to give **25a** (2.60 g, 74%) and **26a** (0.70 g, 20%).

For **25a**: as a white solid, mp 77-81 °C; IR ($CHCl_3$) ν 3480, 1708 cm^{-1}; ^1H NMR (250 MHz) δ 9.38 (d, *J* = 1.0 Hz, 1 H), 4.98 (s, 1 H), 4.89 (d, *J* = 0.6, 1 H), 3.58 (d, J =1.0, 1 H), 2.20 (dt, *J* = 14.9, 2.6 Hz, 1 H), 1.84-2.00 (comp, 2 H), 1.51-1.73 (comp, 3 H), 1.40 (dd, *J* = 3.5, 14.9 Hz, 1 H), 1.18 (s, 6 H), 0.82 (s, 3 H); ^{13}C NMR (63 MHz) δ 203.8, 160.5, 107.5, 78.4, 41.2, 37.4, 37.1, 34.4, 31.3, 29.1, 27.5, 21.8, 17.7; mass spectrum, *m/z* 208.1462 ($C_{13}H_{20}O_2$ requires 208.1463), 193, 179, 161, 147, 135 (base), 121.

For **26a**: as a colorless liquid; IR ($CHCl_3$) ν 3500, 1720 cm^{-1}; ^1H NMR (250 MHz) δ 9.70 (s, 1 H), 5.06 (s, 1 H), 4.94 (s, 1 H), 3.15 (s, 1 H), 1.92-2.08 (comp, 2 H), 1.84 (dt, *J* = 14.9, 3.2, 1 H), 1.43-1.67 (comp, 4 H), 1.23 (s, 3 H), 1.19 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (63 MHz) δ 203.9, 159.6, 107.8, 78.5, 42.6, 37.6, 37.1, 35.5, 30.7, 29.2, 28.2, 22.9, 18.1; mass spectrum, *m/z* 208.1458 ($C_{13}H_{20}O_2$ requires 208.1463), 179, 161, 135 (base), 121.

α-2-Hydroxy-4-*O*-benzyloxy-6-methylene-1,5,5-trimethylbicyclo[2.2.2]octane-β-carboxaldehyde (25b): To a vigorously stirred solution of **24b** (6.91 g, 22.1 mmol) in 25% aqueous THF (180 mL) at 0 °C was added trichloroacetonitrile (14.0 g, 9.7 mL, 96.8 mmol). A buffered solution of H_2O_2 (6.86 mL), which was prepared by combining 30% H_2O_2 (8 mL) and K_2HPO_4 (3.6 g), was added, and the mixture was stirred for 10 min at 0 °C and then at room temperature for 2 h. The mixture was extracted with hexanes (4 x 50 mL), and the combined extracts were washed with water (300 mL), 10% sodium thiosulfite (300 mL), and saturated NaCl (300 mL) and dried ($MgSO_4$). The organic extracts were concentrated under reduced pressure resulting in precipitation of the acetamide by-product, which was removed by suction filtration. The filtrates were further concentrated under reduced pressure to afford 6.02 g (86%) of a 6:1 mixture of epimeric α-hydroxy aldehydes **25b** and **26b** that were separated by HPLC eluting with hexanes/EtOAc (20:1) to afford 4.51 g (65%) of **25b** and 0.75 g of **26b**.

For **25b:** IR (film) ν 3500, 2950, 1720, 1640 cm^{-1}; ^1H NMR (360 MHz) δ 9.40 (s, 1 H), 7.21-7.34 (comp, 5 H), 5.09 (s, 1 H), 4.93 (s, 1 H), 4.50 (d, *J* = 11.7 Hz, 1 H), 4.45 (d, *J* = 11.7 Hz, 1 H), 3.76 (br s, 1 H), 2.10-2.20 (comp, 3 H), 1.82-1.90 (m, 1 H), 1.80 (d, *J* = 14.4 Hz, 1H), 1.35-1.43 (m, 1 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (90 MHz) δ 202.3, 160.2, 139.8, 128.1, 127.1, 126.9, 126.6, 107.8, 79.4, 77.3, 63.5, 42.7, 40.7, 35.7, 29.9, 27.5, 25.0, 24.4, 17.4; mass spectrum, *m/z* 314.1885 ($C_{20}H_{26}O_3$ requires 314.1882), 223, 206, 193, 107, 91 (base).

α-2-Hydroxy-4-*O*-benzyloxy-6-phenylthiomethylene-1,5,5-trimethylbicyclo-[2.2.2]octane-β-carboxaldehyde (25c). To a solution of **24c** (4.20 g, 10.0 mmol) in THF (170 mL) containing Et_4NOH (0.76

mL, 20% in H_2O) and OsO_4 (15 mL, 0.05 M in *tert*-BuOH) at -10 °C was added *tert*-BuOOH (3.04 mL, 70% in H_2O), and the mixture was stirred at -5 °C for 2 h. The reaction was quenched by addition of Me_2S (5 mL) and the resulting mixture stirred at room temperature for 2 h, whereupon the reaction was diluted with saturated NaCl (200 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 250 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes/EtOAc (8:1) to give 3.22 g (76%) of pure **25c**. ^1H NMR (90 MHz) δ 9.58 (s, 1 H), 7.20-7.50 (comp, 10 H), 6.02 (s, 1 H), 4.49 (s, 2 H), 3.84 (s, 1 H), 1.58 (s, 3 H), 1.49 (s, 3 H), 1.40-2.40 (comp, 6 H), 0.82 (s, 3 H); mass spectrum, *m/z* 422.1924 ($C_{26}H_{30}O_3S$ requires 422.1916), 349, 331, 314, 259, 242, 227, 205, 147, 121,107, 91 (base).

2-Ethenyl-6-methylene-1,5,5-trimethylbicyclo[2.2.2]octan-2-ol (27a). *n*-BuLi (17.2 mL of a 2.8 M solution in hexanes, 48.2 mmol) was added dropwise to a suspension of methyl triphenylphosphonium bromide (19.0 g, 53.3 mmol) in THF (150 mL) at -78 °C, and the mixture was stirred for 1 h at 0 °C. After recooling to -78 °C, a solution of aldehyde **25a** (5.2 g, 25.0 mmol) in THF (25 mL) was added dropwise. The reaction was allowed to warm slowly to room temperature (2 h) and stirred for 1 h. The mixture was partitioned between saturated NaCl (150 mL), and the aqueous layer was extracted with Et_2O (3 x 150 mL). The combined organics were washed with brine (100 mL) and dried ($MgSO_4$). The solvents were removed under reduced pressure to furnish the crude product which was purified by column chromatography on silica gel using hexanes/EtOAc (9:1) as the eluent to furnish **27a** (4.5 g, 87%) as a colorless solid: mp 45-46.6 °C; IR ($CHCl_3$) 3585 cm^{-1}; ^1H NMR (90 MHz) δ 5.91 (dd, *J* = 17, 10 Hz, 1 H), 5.12 (dd, *J* = 17, 1.5 Hz, 1 H), 4.90 (dd, *J* = 10, 1.5 Hz, 1 H), 4.88 (s, 1 H), 4.82 (s, 1 H), 1.10-2.15 (comp, 7 H), 1.17 (s, 3 H), 1.10 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR (20 MHz) δ 162.1, 144.9, 109.9, 106.3, 75.0, 42.6, 41.2, 38.2, 37.2, 31.3, 29.2, 27.6, 22.4, 17.8; mass spectrum, *m/z* 206.1673 ($C_{14}H_{22}O$ requires 206.1671), 191, 121 (base).

β-2-Ethenyl-4-*O*-benzyloxy-6-methylene-1,5,5-trimethyl-α-2-bicyclo[2.2.2]-octanol (27b). Prepared from **25b** (2.93 g, 9.3 mmol)according to the procedure described above to provide 2.26 g (78%) of dienol **27b** as a white crystalline solid; mp 63-65 °C; IR (film) ν 3500, 1640 cm^{-1}; ^1H NMR (360 MHz) δ 7.20-7.35 (comp, 5 H), 5.97 (dd, *J* = 17.4, 10.9 Hz, 1 H), 5.15-5.40 (m, 1 H), 4.95-5.05 (comp, 2 H), 4.86 (s, 1 H), 4.48 (d, *J* = 12.6 Hz, 1 H), 4.44 (d, *J* = 12.6 Hz), 1.78-2.16 (comp, 4 H), 1.58-1.68 (m, 1 H), 1.36-1.48 (m, 1 H), 1.24 (s, 3 H), 1.20 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (90 MHz) δ 161.8, 143.9, 140.3, 128.1, 126.8, 126.7, 110.4, 106.6, 76.7, 76.2, 63.3, 42.6, 42.2, 42.1, 29.6, 27.4, 25.4, 24.7, 17.5; mass spectrum *m/z* 312.2097 ($C_{21}H_{28}O_2$ requires 312.2089), 242, 221, 203, 134, 123, 91 (base).

β-2-Ethenyl-4-*O*-benzyloxy-6-phenylthiomethylene-1,5,5-trimethyl-α-2-bicyclo-[2.2.2]-octanol (27c). Prepared from **25c** (2.40 g, 5.7 mmol)according to the procedure described above to give **27c** (1.88 g, 91%). IR (CCl_4) ν 3560 cm^{-1}; ^1H NMR (90 MHz) δ 7.25-7.55 (comp, 10 H), 6.08 (dd, *J* = 17, 11 Hz, 1 H), 5.96 (s, 1 H), 5.24 (d, *J* = 17 Hz, 1 H), 5.07 (d, *J* = 11 Hz, 1 H), 4.50 (s, 2 H), 1.49 (s, 6 H), 1.30-2.30 (comp, 6 H), 0.87 (s, 3 H); ^{13}C NMR (50 MHz) δ 152.4, 143.9, 140.1, 137.9, 129.1, 128.7, 128.2, 126.9, 126.2, 116.0, 110.9, 96.2, 76.6, 76.2, 63.3, 44.1, 42.9, 42.1, 30.0, 29.7, 25.2, 21.1, 18.4, 18.1; mass spectrum, *m/z* 420.2113 ($C_{27}H_{32}O_2S$ requires 420.2123), 402, 329, 311, 293, 254, 159, 105, 91 (base).

8,11,11-Trimethylbicyclo[5.3.1]undec-7-en-3-one (28a). To a suspension of KH (85 mg, 2.12 mmol) in freshly distilled THF (9 mL) was added dropwise a solution of iodine in THF (1 M, 3-4 drops) until the color of iodine persisted for more than a few seconds. The resulting suspension was cooled to 0 °C, and a solution of

dienol **27a** (334 mg, 1.62 mmol) in freshly distilled THF (3.5 mL) was added dropwise. After stirring for 15 min at 0 °C, the mixture was allowed to warm to room temperature, and 18-crown-6 (67 mg, 0.24 mmol) was added in one portion. Stirring was continued for 15 min at room temperature, whereupon the reaction was quenched by careful addition of isopropanol (0.2 mL) followed by sat. NH_4Cl (10 mL). The resulting mixture was extracted with Et_2O (5 x 10 mL), and the combined extracts were dried (Na_2SO_4). Evaporation of the excess solvents under reduced pressure afforded the crude product that was purified by preparative HPLC using 3% EtOAc/hexanes as the eluent to give 292 mg (87%) of **28a** as a waxy solid; IR ($CHCl_3$) 1670 cm^{-1}; ^1H NMR (90 MHz) δ 2.63-2.90 (comp, 1 H), 1.66-2.50 (comp, 12 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (20 MHz) δ 213.1, 138.6, 133.5, 50.2, 44.9, 43.0, 38.3, 28.8, 27.3, 27.0, 26.2, 25.7, 22.4, 20.3; mass spectrum, *m/z* 206.1667 ($C_{14}H_{22}O$ requires 206.1671), 188, 173, 145 (base).

1-*O*-Benzyloxy-8,11,11-Trimethylbicyclo[5.3.1]undec-7-en-3-one (28b). Prepared from **27b** (400 mg, 1.28 mmol) according to the procedure described above (except the rearrangement was conducted for 2 h at room temperature) to give 348 mg (87%) of **28b** as an opaque colorless oil. IR ($CHCl_3$) ν 2910, 1675 cm^{-1}; ^1H NMR (360 MHz) δ 7.14-7.31 (comp, 5 H), 4.47 (d, *J* = 11.9 Hz, 1 H), 4.37 (d, *J* = 11.9 Hz, 1 H), 2.75 (dd, *J* = 10.8, 1.6 Hz, 1 H), 2.32 (d, *J* = 10.8 Hz, 1 H), 2.10-2.35 (comp, 4 H), 1.62-2.10 (comp, 6 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.05 (s, 3 H). ^{13}C NMR (90 MHz) δ 206.7, 140.0, 138.5, 133.7, 128.2, 126.9, 126.6, 85.0, 63.7, 46.1, 43.6, 43.0, 28.5, 26.7, 26.4, 25.8, 25.1, 20.5, 20.2; mass spectrum, *m/z* 312.2100 ($C_{21}H_{28}O_2$ requires 312.2089), 221, 203, 91 (base).

1-*O*-Benzyloxy-6-phenylthio-8,11,11-trimethylbicyclo[5.3.1]undec-7-en-3-one (28c). Prepared from **27c** (838 mg 2.0 mmol) according to the procedure described above (except the rearrangement was conducted at 50 °C for 15 min) to give **28c** (624 mg, 74%); mp 125-126 °C (from hexanes/EtOAc). IR 1670 cm^{-1}; ^1H NMR (360 MHz): 7.15-7.50 (comp, 10 H), 4.54 (d, *J* = 11.8 Hz, 1 H), 4.42, (d, *J* = 11.8 Hz, 1 H), 4.21 (dd, *J* = 12.7, 4.8 Hz, 1 H), 2.89 (d, *J* = 10.9 Hz, 1 H), 2.67 (dq, *J* = 2.9, 13.5 Hz, 1 H), 2.39 (d, *J* = 11.5 Hz, 1 H), 1.70-2.35 (comp, 7 H) 1.73 (s, 3 H), 1.37 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (50 MHz) δ 205.5, 139.8, 137.5, 137.4, 137.0, 132.0, 128.0, 127.1, 126.7, 84.2, 63.9, 50.0, 44.9, 44.6, 32.5, 29.5, 26.4, 26.1, 20.9, 20.2; mass spectrum, *m/z* 420.2129 ($C_{27}H_{32}O_2S$ requires 420.2123), 311 (base), 293, 219, 203, 161, 133, 105, 91.

2-[2(*E*)-Cyanoethenyl]-6-methylene-1,5,5-trimethylbicyclo[2.2.2]octan-2-ol (30). A mixture of **25a** (333 mg, 1.61 mmol) and cyanomethyl triphenylphosphorane (1.21 g, 4.03 mmol) in dry benzene (13 mL) was heated at reflux for 2 h. After cooling to room temperature, the excess solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography using 30% EtOAc/hexanes as eluent to give 343 mg (93%) of **30** as a white solid; m.p. 115-116 °C (from MeOH); IR ($CHCl_3$) 3450, 2240, 1655 cm^{-1}; ^1H NMR (300 MHz) δ 6.78 (d, *J* = 16.2 Hz, 1 H), 5.62 (d, *J* = 16.2 Hz, 1 H), 5.06 (s, 1 H), 4.92 (s, 1 H), 2.05-2.15 (m, 1 H), 1.79-2.00 (m, 3 H), 1.42-1.61 (m, 4 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz) δ 160.6, 160.5, 117.8, 107.5, 96.3, 75.3, 42.5, 40.3, 37.4, 37.0, 31.0, 28.9, 27.0, 21.7, 17.8; mass spectrum, *m/z* 231.1625 ($C_{15}H_{21}NO$ requires 231.1623), 213, 198, 170, 136, 121 (base), 105, 93.

1-*O*-Benzyloxy-5-hydroxy-5-[2'(*E*)-cyanoethenyl]-2,2,4-trimethyl-3-methylenebicyclo-[2.2.2]octane (31). Prepared from **25b** (498 mg, 1.59 mmol) according to the procedure described above for the preparation of **30** to yield 443 mg (83%) of **31** as an amorphous solid. IR (neat) ν 3510, 2260, 1740, 1660 cm^{-1}; ^1H NMR (250 MHz) δ 7.19-7.38 (comp, 5 H), 6.80 (d, *J* = 16.2 Hz, 1 H), 5.64 (d, *J* = 16.2 Hz, 1 H), 5.10 (s, 1 H), 4.94 (s, 1 H), 4.49 (d, *J* = 11.7 Hz, 1 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 1.35-2.18 (comp, 7 H), 1.26 (s, 3 H), 1.21

(s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (63 MHz) δ 160.2, 159.1, 139.8, 128.2, 127.1, 126.7, 117.5, 108.2, 97.3, 76.8, 76.3, 63.5, 42.6, 42.0, 41.5, 29.3, 27.35, 25.0, 24.5, 17.7; mass spectrum, (CI) *m/z* 338 (M+1) 338.2124 ($C_{22}H_{27}NO_2$ + H requires 338.2120), 230, 177, 154 (base).

5-Cyano-8,11,11-trimethyl-bicyclo[5.3.1]undec-7-en-3-one (32). To a suspension of KH (48 mg, 1.2 mmol) in freshly distilled THF (1 mL) was added dropwise at room temperature a solution of **30** (140 mg, 0.6 mmol) in freshly distilled THF (3 mL). After stirring for 10 min at room temperature, the reaction was quenched with saturated NH_4Cl (5 mL). The resulting mixture was extracted with Et_2O (4 x 10 mL), and the combined Et_2Oeal extracts were dried ($MgSO_4$), filtered and concentrated. Flash chromatography of the crude product using first 10% EtOAc/hexanes and then 20% EtOAc/hexanes gave 130 mg (93%) of **32** as an amorphous solid. IR (neat) ν 2950, 2240, 1700, 1480 cm^{-1}. ^{1}H NMR (300 MHz) δ 3.24-3.33 (m, 1 H), 2.96 (dt, *J* = 1.6, 12.6 Hz, 2 H), 2.83 (dd, *J* = 5.7, 14.3 Hz, 1 H), 2.51 (dd, *J* = 12.2, 14.3 Hz, 1 H), 2.33 (br d, *J* = 12.3, 1 H), 2.04-2.15 (comp, 4 H), 1.98-1.82 (m, 1 H), 1.65-1.73 (m, 1 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.07 (s, 3 H); mass spectrum *m/z* 231.1625 (M^+) ($C_{15}H_{21}NO$ requires 231.1623), 213, 198, 170, 162 (base), 143, 135, 119, 105, 91, 41.

1-*O*-Benzyloxy-5-cyano-8,11,11-trimethylbicyclo[5.3.1]undec-7-en-3-one (33). To a suspension of KH (12.4 mg, 0.31 mmol) in THF (1.5 mL) was added a solution of **31** (40 mg, 0.124 mmol) in THF (1.0 mL) at 0 °C. After 25 min the reaction was stopped by addition of saturated NH_4Cl (2.5 mL). Subsequently the mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by flash chromatography using hexanes/EtOAc (10:1) as eluent to give **33** (37 mg, 93%) as a white amorphous solid. IR (CCl_4) ν 2990, 1690 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.21-7.38 (comp, 5 H), 4.55 (d, *J* = 11.8 Hz, 1 H), 4.42 (d, *J* = 11.8 Hz, 1 H), 3.40 (m, 1 H), 2.16-2.73 (comp, 6 H), 1.72-1.97 (comp, 2 H), 1.45 (s, 3 H), 1.32 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR (75 MHz) δ 199.0, 139.4, 138.3, 135.1, 128.3, 127.2, 126.6, 120.6, 84.8, 64.1, 45.0, 44.0, 30.3, 29.7, 28.5, 28.2, 25.9, 24.7, 20.5, 19.7; mass spectrum, (CI) *m/z* 338 (M+1, base) 338.2128 ($C_{22}H_{27}NO_2$+H requires 338.2120), 246, 187, 160, 91.

4,8,11,11-Tetramethylbicyclo[5.3.1]undec-7-en-3-one (38a,b). A solution of alcohol **27a** (6.0 g, 29.0 mmol) in THF (50 mL) was added dropwise to a suspension of KH (4.2 g of a 35% dispersion in mineral oil, 35.2 mmol) in THF (157 mL) at 0 °C. After stirring at 0 °C for 5 min and then at room temperature for 15 min, 18-crown-6 (1.1 g, 4.1 mmol) was added in one portion. Stirring was continued at room temperature for 40 min and then cooled to -78 °C, whereupon MeI (3.6 mL, 58.0 mmol) was added in one portion. The reaction was then stirred at room temperature for 12 h. The mixture was partitioned between brine (200 mL) and Et_2O (3 x 200 mL), and the organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure to furnish a residue that was purified by preparative HPLC using hexanes/EtOAc (20:1) to give **38a** (1.3 g, 21%) and **38b** (2.5 g, 39%).

For **38a**: IR (film) ν 1685 cm^{-1}; ^{1}H NMR (360 MHz) δ 2.71 (dd, *J* = 11.2, 2.2 Hz, 1 H), 2.42 (dd, *J* = 6.5, 12.9 Hz, 1 H), 2.40 (dd, *J* = 6.5, 12.9 Hz, 1 H), 2.16 (br d, *J* = 12.9 Hz, 1 H), 2.15 (br d, *J* = 12.8 Hz, 1 H), 1.70-2.10 (comp, 6 H), 1.67 (dd, *J* = 11.2, 4.7 Hz, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.06 (s, 3 H), 0.96 (d, *J* = 6.91 Hz, 3 H); ^{13}C NMR (90 MHz) δ 214.0, 139.7, 133.0, 49.9, 47.6, 39.1, 38.8, 35.8, 28.2, 27.3, 25.6, 25.1, 21.6, 20.3, 19.1; mass spectrum, *m/z* 220.1822 ($C_{15}H_{24}O$ requires 220.1827), 202, 187, 159, 151, 119, 105 (base), 91, 79, 41.

For **38b**: IR (film) ν 1705, 1665 cm^{-1}; ^{1}H NMR (360 MHz) δ 2.90 (dd, *J* = 11.2, 5.3 Hz, 1 H), 2.81 (ddq, *J* = 18.3, 3.1, 6.6 Hz, 1 H), 2.35 (br dd, *J* = 13.1, 5.9 Hz, 1 H), 2.22 (dd, *J* = 11.8, 5.1 Hz, 0.66 H), 2.20 (dd, *J* = 11.8, 5.0 Hz, 0.34 H), 1.80-2.15 (comp, 6 H), 1.73 (m, 0.66 H), 1.59 (dd, 0.34 H, *J* = 13.1, 5.0 Hz),

1.44 (s, 3 H), 1.43 (s, 3 H), 1.05 (s, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (90 MHz) δ 217.9, 136.6, 134.2, 50.6, 49.6, 46.1, 37.9, 37.0, 29.8, 28.2, 27.6, 25.1, 24.1, 20.3, 18.6; mass spectrum, *m/z* 220.1830 ($C_{15}H_{24}O$ requires 220.1827), 202, 187, 159 (base), 151, 121, 107, 91, 79.

4-Phenylselenyl-8,11,11-trimethylbicyclo[5.3.1]undec-7-en-3-ones (39a,b). A solution of alcohol **27a** (1.96 g, 9.5 mmol) in THF (10 mL) was added slowly to a suspension of KH (1.31 g of a 35% dispersion in mineral oil, 11.4 mmol) in THF (50 mL) at 0 °C. The resulting mixture was stirred for 5 min at 0 °C and then at room temperature for 10 min, whereupon 18-crown-6 (0.35 g, 1.3 mmol) was added in one portion. After stirring for an additional 45 min, diphenyldiselenide (4.48 g, 14.3 mmol) was added in one portion, and after 3 h the reaction was quenched with isopropanol (0.5 mL). The mixture was partitioned between saturated brine (100 mL) and Et_2O (3 x 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to furnish a residue that was purified by column chromatography on silica gel. Elution with hexanes gave diphenyldiselenide, and then elution with hexanes/EtOAc (20:1) gave a mixture (15:85) of epimeric phenylselenides (2.94 g, 89%), which were separated by HPLC eluting with hexanes/EtOAc (50:1) to provide the minor epimer **39a** as a pale yellow oil and the major epimer **39b** as a pale yellow solid.

For **39a**: IR (film) ν 1680 cm^{-1}; ^{1}H NMR (360 MHz) δ 7.57 (comp, 2 H), 7.28 (comp, 3 H), 4.15 (dd, J = 12.5, 3.0 Hz, 1 H), 2.81 (dd, J = 10.0, 5.7 Hz, 1 H), 2.52 (m, 1 H), 2.45 (m, 1 H), 2.20 (dddd, J = 14.1, 12.2, 5.1, 4.0 Hz, 1 H), 1.88-2.15 (comp, 5 H), 2.01 (dd, J = 10.0, 2.3 Hz, 1 H), 1.72 (m, 1 H), 1.45 (s, 3 H), 1.39 (s, 3 H), 1.03 (s, 3 H); 13C NMR (90 MHz) δ 212.4, 135.8, 135.5, 135.0, 129.6, 129.1, 127.9, 54.2, 50.7, 49.2, 37.8, 36.0, 30.0, 28.5, 27.6, 26.3, 24.2, 20.4; mass spectrum, *m/z* 362.1140 ($C_{20}H_{26}O^{80}Se$ requires 362.1148), 205 (base), 184, 135, 119, 105, 91, 77, 55.

For **39b**: mp 84-85 °C; IR (film) ν 1662 cm^{-1}; ^{1}H NMR (360 MHz) δ 7.52 (ddd, J = 6.2, 1.7, 1.7 Hz, 2 H), 7.28 (comp, 3 H), 3.43 (dd, J = 13.2, 4.8 Hz, 1 H), 2.85 (dd, J = 12.0, 0.5 Hz, 1 H), 2.54 (m, 1 H), 2.16-2.25 (comp, 3 H), 1.60-2.15 (comp, 5 H), 1.82 (dd, J = 12.0, 4.5 Hz, 1 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (90 MHz) δ 203.6, 138.2, 135.7, 134.6, 129.0, 128.5, 128.0, 52.7, 49.6, 39.1, 38.8, 33.3, 28.3, 27.3, 26.4, 25.0, 21.6, 20.3; mass spectrum, *m/z* 362.1154 ($C_{20}H_{26}O_{80}Se$ requires 362.1148), 205 (base), 184, 135, 119, 105, 91, 77, 55. Anal. Calcd. for $C_{20}H_{26}OSe$: C, 66.47; H, 7.25. Found: C, 66.58; H, 7.39.

8,11,11-Trimethylbicyclo[5.3.1]undec-4,7-dien-3-one (35). A solution containing MCPBA (410 mg, 2.0 mmol) and the mixture of epimeric selenides **39a,b** (595 mg, 1.6 mmol) in CCl_4 (14 mL) was stirred for 2 h at -15 °C. Diisopropylamine (0.5 mL) was added, and the solution was transferred by cannula into a refluxing solution of CCl_4 (38 mL) and diisopropylamine (2 mL). After 30 min, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using hexanes/EtOAc (20:1) to give **35** (228 mg, 70%) as a sticky colorless solid: IR ($CHCl_3$) ν 1652 cm^{-1}; ^{1}H NMR (500 MHz) δ 5.71 (dt, J = 11.4, 2.9 Hz, 1 H), 5.54 (dt, J = 11.4, 2.0 1 H), 2.87 (dt, J = 18.8, 2.9 Hz, 1 H), 2.83 (dd, J = 11.5, 5.3 Hz, 1 H), 2.63 (br d, J = 18.8 Hz, 1 H), 2.05 (comp, 2 H), 2.00 (dd, J = 11.5, 3.3 Hz, 1 H), 1.88 (m, 1 H), 1.79 (m, 1 H), 1.67 (m, 1 H), 1.26 (s, 3 H), 1.25 (s, 3 H), 1.03 (s, 3 H); ^{13}C NMR (125 MHz) δ 208.2, 136.1, 133.9, 132.4, 131.4, 48.9, 48.6, 37.2, 29.7, 27.8, 26.5, 25.9, 23.1, 19.2; mass spectrum, *m/z* 204.1523 ($C_{14}H_{20}O$ requires 204.1514), 186, 171, 143 (base), 128, 115, 91.

4-Formyl-8,11,11-trimethylbicyclo[5.3.1]undec-7-en-3-one (40). A mixture of freshly prepared powdered sodium methoxide (290 mg, 5.37 mmol), ethyl formate (0.45 mL, 5.58 mmol), and ketone **28a** (110 mg, 0.534 mmol) in dry benzene (5 mL) was stirred for 15 h. The reaction was quenched by pouring into sat. NH_4Cl (10

mL), and the resulting mixture was extracted with Et_2O (5 x 10 mL). The combined Et_2Oeal extracts were dried (Na_2SO_4), filtered and concentrated, and the residue was purified by HPLC using 3% EtOAc/hexanes as the eluent to afford 96 mg (76%) of formyl ketone **40**, mp 57-58 °C; IR (neat) 3600-3100, 1740, 1640, 1585 cm^{-1}; ^1H NMR (300 MHz) δ 14.36 (d, J = 9.9 Hz, 1 H), 7.12 (d, J = 9.6 Hz, 1 H), 2.61 (d, J = 11.7 Hz, 1 H), 1.75-2.50 (comp, 10 H), 1.28 (s, 3 H), 1.23 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz) δ 205.0, 165.1, 137.2, 132.1, 113.4, 48.5, 42.9, 38.7, 29.0, 28.5, 27.9, 27.7, 25.0, 21.4, 20.3; mass spectrum, *m/z* 234.1625 ($C_{15}H_{22}O_2$ requires 234.1619), 216, 173, 161, 145, 135, 121 (base), 109, 91, 77.

4-Formyl-4,8,11,11-tetramethylbicyclo[5.3.1]undec-7-en-3-one (41). A suspension of sodium hydride (15 mg, 0.635 mmol) containing **40** (135 mg, 0.576 mmol) THF (2 mL) was stirred for 30 min at 0 °C. Methyl iodide (0.07 mL, 1.15 mmol) was added, and the stirring was continued for 10 min at 0 °C and 2 h at room temperature. The reaction was quenched by the adding solid $NaHCO_3$. The resulting mixture was then filtered and concentrated, and the residue was purified by HPLC using 3% EtOAc/hexanes as the eluent to furnish 125 mg (87%) of **41**, mp 55-57 °C; IR ($CHCl_3$) 1735, 1685, 1655 cm^{-1}; ^1H NMR (300 MHz) δ 10.19 (s, 1 H), 2.80 (d, J = 11.7 Hz, 1 H), 1.60-2.55 (comp, 10 H), 1.37 (s, 3 H), 1.23 (s, 3 H), 1.06 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz) δ 211.1, 204.5, 138.9, 134.3, 59.7, 49.6, 41.1, 39.1, 33.8, 28.4, 27.3, 25.0, 23.8, 22.8, 21.4, 20.8; mass spectrum, *m/z* 248.1774 ($C_{16}H_{24}O_2$ requires 248.1776), 230, 202 (88.2), 201 (base), 187, 178, 159, 145, 133, 121, 109, 91.

8,11,11-Trimethylbicyclo[5.3.1]undec-7-en-3,9-dione (37). 3,5-Dimethylpyrazole (96 mg, 0.98 mmol) was added in one portion to a suspension of CrO_3 (98 mg, 0.98 mmol) and pulverized 3Å-molecular sieves (10 mg) in CH_2Cl_2 (1.25 mL) at -20 °C. After stirring for 20 min, a solution of ketone **28a** (10 mg, 0.05 mmol) in CH_2Cl_2 (0.25 mL) was added, and the mixture was stirred at -20 °C for 12 h. A solution of 1 N NaOH (2 mL) was added, and the mixture was then extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with 1 N HCl (10 mL) and saturated brine (10 mL), and dried ($MgSO_4$). The solvents were removed under reduced pressure, and the residue was purified by preparative HPLC using hexanes/EtOAc (2:1) to provide **37** (10 mg, 91%) as a colorless oil: IR (film) ν 1730, 1680 cm^{-1}; ^1H NMR (500 MHz) δ 3.00 (dd, J = 13.2, 5.3 Hz, 1 H), 2.88 (dd, J = 21.1, 7.9 Hz, 1 H), 2.59 (d, J = 21.1 Hz, 1 H), 2.36-2.58 (comp, 4 H), 2.07-2.21 (comp, 3 H), 2.10 (dd, J = 13.2, 5.3 Hz, 1 H), 1.67 (s, 3 H), 1.52 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (125 MHz) δ 213.0, 198.3, 159.7, 135.5, 46.4, 44.9, 42.9, 39.3, 39.2, 33.4, 27.6, 26.2, 25.6, 12.9; mass spectrum, *m/z* 220.1467 ($C_{14}H_{20}O_2$ requires 220.1463), 178, 163, 150, 135, 121, 107, 91, 79, 55, 41 (base).

2-(1-Hydroxyethyl)-6-methylene-1,5,5-trimethylbicyclo[2.2.2]octan-2-ol. To a solution of aldehyde **25a** (1.25 g, 6.0 mmol) in THF (23 mL) at -20 °C was added dropwise MeLi (12.8 mL of a 1.4 M solution in Et_2O, 18 mmol). The reaction mixture was allowed to warm to room temperature over 30 min. The solution was then cooled to 0 °C, and a saturated NH_4Cl solution (23 mL) was added. After stirring for 5 min, CH_2Cl_2 (70 mL) and H_2O (50 mL) were added, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture (10:1) of diastereomeric alcohols (1.34 g, 99%) as an oil. IR ($CHCl_3$) ν 3550 cm^{-1}; ^1H NMR (250 MHz) δ (for major isomer) 4.87 (s, 1 H), 4.86 (s, 1 H), 3.74 (dq, J = 1.5, 6.4 Hz, 1 H), 2.47 (s, 1 H), 2.09 (d, J = 1.5 Hz, 1 H), 1.96-1.00 (m, 7 H), 1.12 (s, 3 H), 1.09 (d, J = 6.4 Hz, 3 H), 0.98 (s, 3 H); ^{13}C NMR (90 MHz) δ (for major isomer) 162.3, 106.6, 75.0, 71.5, 43.0, 37.7, 37.0, 35.3, 31.6, 29.6, 28.9, 21.9, 18.8, 18.7; mass spectrum, *m/z* 224.1780 ($C_{14}H_{24}O_2$ requires 224.1776), 206, 191, 179, 135, 121 (base).

1-(2-Hydroxy-6-methylene-1,5,5-trimethylbicyclo[2.2.2]octan-2-yl)ethanone (42). To a stirred solution of DMSO (1.9 g, 24.3 mmol) in CH_2Cl_2 (20 mL) was added slowly a solution of trifluoroacetic anhydride (2.57 mL, 18.2 mmol) in CH_2Cl_2 (15 mL). After stirring at that temperature for 15 min, the mixture of diastereomeric alcohols from the preceding experiment (1.34 g, 5.97 mmol) was added dropwise, and stirring was continued for 4 h between-40 and-50 °C. The solution was then cooled to -60 °C, and triethylamine (4.92 g, 48.6 mmol) was added dropwise. After stirring for 10 min, the cooling bath was removed, and the reaction was quenched by addition of saturated NH_4Cl (50 mL) and H_2O (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide a residue that was purified by flash chromatography on silica gel using hexanes/EtOAc (10:1) as the eluent to give 1.13 g (85%) of **42**. IR ($CHCl_3$) ν 3430, 1695 cm^{-1}; ^1H NMR (250 MHz) δ 4.98 (s, 1 H), 4.91 (s, 1 H), 4.45 (s, 1 H), 2.05-2.26 (m, 1 H), 2.17 (s, 3 H), 1.05-1.98 (comp, 6 H), 1.22 (s, 3 H), 0.73 (s, 3 H); ^{13}C NMR (63 MHz) δ 212.0, 161.5, 107.5, 81.9, 42.4, 37.4, 37.1, 36.8, 32.2, 29.2, 28.6, 26,7, 21.7, 17.9; mass spectrum, *m/z* 222.1615 ($C_{14}H_{22}O$ requires 222.1620), 204, 179, 135 (base).

2-(1-Hydroxy-5-hexenyl)-6-methylene-1,5,5-trimethylbicyclo[2,2,2]octanol. To a freshly prepared solution of pent-4-enyllithium (9 mmol) in dry Et_2O (22.4 mL), **25a** (850 mg, 4.08 mmol) was added dropwise at -78 °C. After stirring at -78 °C for 1 h, saturated aqueous NH_4Cl (10 mL) and H_2O (5 mL) were added. The mixture was extracted with Et_2O (3 x 3 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide a residue that was purified by flash chromatography on silica gel using hexanes/EtOAc (6:1) as the eluent to give 934 mg (84%) as a mixture of diastereomeric alcohols. For the major isomer: IR (CCl_4) *v* 3500, 3080, 2930, 1710, 1645 cm^{-1}; ^1H NMR (250 MHz) δ 5.76 (ddt, *J* = 6.6, 10.0, 20.0 Hz, 1 H), 5.00 (dd *J* = 1.8, 3.6 Hz, 1 H), 4.86-4.96 (comp, 3 H), 3.52 (dd, *J* = 1.6, 10.0 Hz, 1 H), 0.75-2.10 (comp, 11 H), 1.13 (s, 3 H), 1.06 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 162.5, 161.6, 138.7, 114.7, 109.5, 106.6, 76.1, 75.8, 43.1, 37.8, 37.1, 35.8, 33.6, 31.7, 31.3, 29.9, 29.0, 28.9, 25.6, 22.0, 18.9; mass spectrum *m/z* 278.2241 ($C_{18}H_{30}O_2$ requires 278.2245), 260, 135, 121 (base).

2-(5-Hexenoyl)-6-methylene-1,5,5-trimethylbicyclo[2,2,2]octanol (43). A solution of DMSO (3.7 g, 47.4 mmol) in CH_2Cl_2 (5 mL) was added to a solution of oxalyl chloride (3.0 g, 23.7 mmol) in CH_2Cl_2 (20 mL) at -50 °C. The reaction mixture was stirred for 2 min, and a mixture of the diastereomeric alcohols (990 mg, 3.56 mmol) prepared in the preceding experiment was added within 10 min. Stirring was continued at -50 °C for 15 min, whereupon Et_3N (10.9 mL, 108 mmol) was added and stirring continued for 5 min. The cooling bath was removed, and the mixture was allowed to warm to 0 °C and saturated aqueous NH_4Cl (40 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide a residue that was purified by flash chromatography on silica gel using hexanes/EtOAc (19:1) as the eluent to give 980 mg (99%) of **43**. IR (CCl_4) *v* 3430, 3080, 2950, 1690 cm^{-1}; ^1H NMR (250 MHz) δ 5.75 (ddt, *J* = 6.7, 10.3, 17.0 Hz, 1 H), 4.90-5.05 (comp, 4 H), 4.48 (s, 1 H), 2.40-2.61 (m, 2 H), 2.30 (dd, *J* = 1.9, 12.8 Hz, 1 H), 1.05-2.06 (comp, 14 H), 1.26 (s, 3 H), 1.23 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 214.1, 151.5, 137.9, 115.3, 107.3, 81.8, 42.6, 37.7, 37.4, 37.2, 36.9, 33.1, 32.2, 29.3, 28.7, 23.9, 21.7, 18.0; mass spectrum *m/z* 276.2096 ($C_{18}H_{30}O_2$ requires 276.2089), 258, 204, 135 (base), 121.

2-(2-Cyano-1-methylethenyl)-6-methylene-1,5,5-trimethylbicyclo[2.2.2]octan-2-ol (44). A suspension of NaH (125 mg of 55% suspension in mineral oil) and diethyl cyanomethylphosphonate (508 mg, 2.87

mmol) in DME (5 mL) was stirred for 30 min at room temperature, and then the mixture was added to a solution of **42** (290 mg, 1.30 mmol) in DME (6.5 mL). After stirring at room temperature for 1.5 h, the reaction was quenched by adding saturated NH_4Cl (10 mL) and H_2O (10 mL), and the aqueous mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (5:1) to give 260 mg (81%) of **44**. IR ($CHCl_3$) ν 3430, 2235, 1730, 1635 cm^{-1}; ^1H NMR (250 MHz) δ 5.61 (s, 1H), 4.93 (s, 1 H), 4.89 (s, 1 H), 2.17 (br dt, *J* = 2.2, 14.8 Hz, 1 H), 2.04 (s, 3 H), 1.95-1.80 (comp, 2 H), 1.60-1.75 (comp, 2 H), 1.50 (m, 1 H), 1.39 (dd, *J* = 4.1, 14.9 Hz, 1 H), 1.10-1.28 (m, 1 H), 1.19 (s, 3 H), 1.18 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (63 MHz) δ 171.2, 169.6, 161.0, 107.8, 96.6, 60.4, 43.4, 39.9, 37.4, 37.3, 32.3, 29.9, 28.6, 21.9, 18.1, 14.2; mass spectrum, (CI) *m/z* 246.1866 (base) ($C_{16}H_{23}NO$+H requires 246.1858), 228, 179, 136.

2-(2-Cyano-1-(4-pentenyl)-ethenyl-6-methylene-1,5,5-trimethylbicyclo[2,2,2]octan-2-ol (45). A suspension of NaH (28 mg, 1.16 mmol) and diethyl cyanomethylphosphonate (205 mg, 1.16 mmol) in DME (2.3 mL) was stirred for 30 min at room temperature, whereupon a solution of **43** (40 mg, 0.14 mmol) in DME (1.5 mL) was added and the reaction stirred at room temperature for 4 d. Saturated aqueous NH_4Cl (5 mL) and water (2 mL) were added, and the resulting mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide a residue that was purified by flash chromatography on silica gel using hexanes/EtOAc (9:1) as the eluent to give 15 mg (36%, 94% based upon recovered starting material) of **45** as a mixture of nitriles and 25 mg (62%) of recovered starting material. IR (CCl_4) *v* 3440, 3080, 2940, 2235, 1690, 1640 cm^{-1}; ^1H NMR (250 MHz) δ 5.68-5.87 (m, 1 H), 4.86-5.07 (comp, 4 H), 3.51-3.58 (m, 1 H), 2.81 (dd, *J* = 8.6, 14.1 Hz, 1 H), 2.68 (dd, *J* = 3.1, 10.7 Hz, 1 H), 0.80-2.54 (comp, 21 H); mass spectrum *m/z* 300.2326 ($C_{20}H_{29}NO$ + H requires 300.2327), 282, 254, 208 (base), 121.

5-Cyano-4,11,11-trimethylbicyclo[5.3.1]undec-7-en-3-one (46). To a suspension of KH (40 mg, 1.0 mmol) in THF (2 mL) at 0 °C was added **44** (98 mg, 0.40 mmol) in THF (1 mL). The reaction was quenched after 2 min by addition of a saturated NH_4Cl solution (2.5 mL). The mixture was diluted with H_2O (10 mL), and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using hexanes/EtOAc (5:1) as the eluent to give 88 mg (90%) of **46**. IR ($CHCl_3$) ν 2240, 1685 cm^{-1}; ^1H NMR (250 MHz) δ 3.82 (dt, *J* = 5.0, 12.2 Hz, 1 H), 2.76 (t, *J* = 12.2 Hz, 1 H), 2.64 (br d, *J* = 10.7 Hz, 1 H), 2.52 (ddd, *J* = 1.4, 5.1, 13.7 Hz, 1 H), 2.40 (dq, *J* = 4.7, 7.0 Hz, 1 H), 1.70-2.08 (comp, 6 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 1.20 (d, *J* = 7.0 Hz, 3 H), 1.04 (s, 3 H); ^{13}C NMR (63 MHz) δ 212.0, 161.5, 107.5, 81.9, 42.4, 37.4, 37.1, 36.8, 32.2, 29.2, 28.6, 26,7, 21.7, 17.9; mass spectrum, (CI) *m/z* 246.1869 (base) ($C_{16}H_{23}O$+H requires 246.1858), 228, 200, 154.

4-(4-Acetoxybutyl)-5-cyano-4,8,11,11-tetramethyl-bicyclo[5.3.1]undec-7-en-3-one (47). To a suspension of KH (40 mg, 1.0 mmol) in THF (2 mL) at 0 °C was added **44** (98 mg, 0.40 mmol) in THF (1 mL). After stirring for 1 min, 4-iodobutylacetate (387 mg, 1.6 mmol) in THF (0.5 mL) was added, and the mixture was stirred for 10 min at 0 °C. The reaction was quenched by the addition of saturated NH_4Cl (2.5 mL) and then H_2O (10 mL). The resulting mixture was extracted with Et_2O (4 x 15 mL), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc (5:1) as the eluent to give 132 mg (92%) of **47**. IR ($CHCl_3$) ν 2230, 1730, 1695 cm^{-1}; ^1H NMR (250 MHz) δ 3.94 (t, *J* = 6.6 Hz, 2 H), 3.46 (dd, *J* =5.0, 12.6 Hz, 1 H), 2.78 (t, *J* = 13.6 Hz, 1 H), 2.72 (dd, *J* = 2.0,

12.2 Hz, 1 H), 2.52 (dd, J = 4.5, 13.5 Hz, 1 H), 0.70-2.01 (comp, 11 H), 1.94 (s, 3 H), 1.40 (s, 3 H), 1.30 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (63 MHz) δ 207.8, 171.2, 139.3, 132.7, 120.6, 63.8, 52.4, 48.1, 40.9, 39.8, 39.1, 38.7, 29.1, 28.6, 27.5, 24.7, 21.7, 21.1, 20.9, 20.0, 14.5; mass spectrum, (CI) *m/z* 360.2544 ($C_{22}H_{33}NO_3$+H requires 360.2548), 342, 246 (base), 190, 159.

5-Cyano-4-(4-pentenyl)-4,8,11,11-tetramethylbicyclo[5.3.1]undec-7-en-3-one (48). To a suspension of KH (23 mg, 0.58 mmol) in THF (2 mL) at 0 °C was added **42** (72 mg, 0.29 mmol) in THF (1 mL). After 3 min 5-bromo-1-pentene (180 mg, 1.2 mmol) was added, and stirring was continued for 20 min. Saturated aqueous NH_4Cl (5 mL) and water (2 mL) were then added, and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide a residue that was purified by flash chromatography on silica gel using hexanes/EtOAc (9:1) as the eluent to give 85 mg (84%) of **48.** IR (CCl_4) ν 3080, 2940, 2230, 1730, 1645 cm^{-1}; ^{1}H NMR (250MHz) δ 5.66 (ddt, J = 6.7, 10.3, 16.9 Hz, 1 H), 4.87-4.98 (m, 2 H), 3.47 (dd, J = 5.0, 12.7 Hz, 1 H), 2.79 (t, J = 13.6 Hz, 1H), 2.72 (dd, J = 2.7, 11.9 Hz, 1 H), 2.53 (dd, J = 4.7, 13.7 Hz, 1 H), 0.78-2.08 (comp, 12 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 1.11 (s, 3 H), 1.03 (s, 3H); ^{13}C NMR (62.5 MHz) δ 207.5, 139.3, 137.7, 132.7, 120.6, 115.2, 52.4, 48.2, 41.1, 39.9, 39.0, 38.8, 33.6, 29.2, 28.8, 27.6, 24.8, 22.6, 21.8, 21.2, 14.7; mass spectrum *m/z* 314.2486 ($C_{21}H_{31}NO$+H requires 314.2484), 296, 222 (base), 200.

5-Cyano-4-(4-pentenyl)-4,8,11,11-tetramethylbicyclo[5.3.1]undec-7-en-2-one (49). To a suspension of KH (10 mg, 0.25 mmol) in THF (2 mL) at 0 °C was added **45** (12 mg, 0.04 mmol) in THF (1 mL). After 1 min MeI was added, and stirring was continued for 10 min. Saturated aqueous NH_4Cl (5 mL) and water (1 mL) were added, and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a residue that was purified by flash chromatography on silica gel using hexanes/EtOAc (6:1) as the eluent to give 11 mg (88%) of **49**. IR (CCl_4) ν 3080, 2940, 2230, 1730, 1645 cm^{-1}; ^{1}H NMR (250 MHz) δ 5.83 (ddt, J = 6.6, 10.2, 17.0 Hz, 1 H), 4.93-5.08 (m, 2 H), 3.53 (dd, J = 4.6, 12.9 Hz, 1 H), 2.74-2.86 (m, 2 H), 2.53 (dd, J = 3.1, 13.9 Hz, 1 H), 0.85-2.12 (comp, 12 H), 1.52 (s, 3 H), 1.37 (s, 3 H), 1.19 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 209.7, 139.2, 138.3, 132.3, 120.6, 114.7, 50.8, 48.0, 40.9, 39.7, 38.8, 34.7, 30.5, 29.5, 28.6, 27.7, 24.8, 24.4, 22.6, 22.0, 21.2; mass spectrum *m/z* 314.2479 ($C_{21}H_{31}NO$+H requires 314.2484) (base).

5-Cyano-4-[(4'-trimethylstannyl)pent-4'-enyl]-8,11,11-trimethylbicyclo[5.3.1]undec-7-ene-3-one (50). To a stirred suspension of KH (15 mg, 0.37 mmol) in THF (2.5 mL) was added **30** (72 mg, 0.32 mmol) in THF (0.5 mL) at room temperature. After stirring for 15 min, 5-iodo-2-trimethylstannylpentene (126 mg, 0.35 mmol) in THF (1 mL) was added, and the resulting solution was stirred for 2 h at room temperature. The reaction was quenched with saturated NH_4Cl.(3 mL), and the organic layer was separated. The aqueous phase was extracted with Et_2O (3 x 10 mL), and the combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried ($MgSO_4$). Evaporation of the solvents under reduced pressure gave a residue that was purified by flash chromatography on silica using hexanes/EtOAc (9:1) and then hexanes/EtOAc (4:1) as eluents to give a mixture (2:1) (101 mg, 76%) of **50** and a diastereoisomer of unknown relative stereochemistry as major products.

For **50**: IR (neat) ν 2950, 2240, 1690, 1480 cm^{-1}; ^{1}H NMR (250 MHz) δ 5.60-5.64 (m, 1 H), 5.10-5.16 (m, 1 H), 3.17-3.21 (m, 1 H), 2.50-2.79 (comp, 3 H), 1.74-2.30 (comp, 9 H), 1.22-1.45 (comp, 4 H), 1.45 (s, 3 H), 1.32 (s, 3 H), 1.07 (s, 3 H), 0.12 (s, 9 H). ^{13}C NMR (63 MHz) δ 206.1, 154.5, 138.5, 134.9, 125.1, 120.9, 53.6,

49.1, 40.2, 38.6, 35.9, 30.8, 30.4, 28.0, 27.3, 25.6, 24.8, 21.2, 20.5,-9.5; mass spectrum, *m/z* 463.1885 ($C_{23}H_{37}NOSn$ requires 463.1897), 448, 446, 430 (base), 428, 403, 401, 286, 253, 165, 91.

9-Cyano-3-hydroxy-12,15,15-trimethyl-4-methylenetricyclo[9.3.1.0^{3,8}]pentadec-11-ene (51). To a stirred solution of **50** (110 mg, 0.24 mmol) in THF (4 mL) was added MeLi (0.35 mL of 1.4 M in Et_2O, 0.48 mmol) at -78 °C. After stirring for 15 min, a saturated solution of NH_4Cl (3 mL) was added, and the mixture allowed to warm to room temperature. The aqueous phase was separated and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a solid residue that was purified by chromatography on silica using hexane/EtOAc (9:1) and hexane/EtOAc (4:1) as eluents to give a mixture (4:1) (42 mg; 58%) of **51** and a stereoisomer of unknown stereochemistry. The structure of **51** was established by X-ray analysis.

For **51**: as a white solid, mp 144-146 °C (from MeOH); IR (neat) ν 3500, 2950, 2250, 1450 cm^{-1}; ^{1}H NMR (500 MHz) δ 4.83 (s, 1 H), 2.51-2.64 (m, 2 H), 2.48 (m, 1 H), 2.38-2.44 (m, 2 H), 1.98 (dd, *J* = 1.6, 1.3 Hz, 2 H), 1.79-2.18 (m, 6 H), 1.68 (s, 3 H), 1.54 (m, 2 H), 1.19 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR (125 MHz) δ 155.4, 135.8, 133.5, 122.2, 109.2, 78.5, 45.5, 42.2, 39.4, 38.3, 33.2, 31.2, 31.0, 29.5, 29.0, 25.8, 25.7, 23.4, 22.2, 21.3; mass spectrum *m/z* 299.2244 ($C_{20}H_{29}NO$ requires 299.2249), 284, 281, 266, 256, 238, 226, 198, 179, 135, 109, 91 (base), 69, 55, 41.

Acknowledgment. We are grateful to the Robert A. Welch Foundation and the National Institutes of Health for their support of this research.

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(*Received in USA* 4 *November* 1994; *accepted* 24 *January* 1995)