[2 + 3] and [3 + 4] Annulation of Enones. Enantiocontrolled Total Synthesis of (−)-Retigeranic Acid†

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Abstract: The lithium dienolates of ethyl 2-bromocrotonate and of other, more highly substituted α-bromocrotonates underwent smooth addition to enones to provide, in one step, the corresponding vinylcyclopropanes in excellent yields. The vinylcyclopropanes were subjected to several modes of rearrangement: thermolysis to afford annulated cyclopentenes in an overall [2 + 3] annulation sequence; conversion to enol ethers to give, via the Cope rearrangement of divinylcyclopropanes, bicyclo[3.2.*n*] systems; and nucleophilic opening with trimethylsilyl iodide to afford, at low temperatures, intermediate allylic iodides that were cyclized to annulated cyclopentenes under basic conditions. The stereochemical details of the vinylcyclopropanation and the cyclopentene rearrangement were investigated. The application of this process was realized by the convergent and enantiocontrolled total synthesis of (−)-retigeranic acid. The scope, the limitation, and some future applications of this methodology are indicated.

The development of synthetic methodologies that allow for efficient construction of cyclopentanoids has been the focus of the synthetic community throughout the last decade. Many approaches to functionalized cyclopentanes have been reported,[2] and these can be divided into several categories: [2 + 3],[3] [4 + 1],[4] [2 + 2 + 1],[5] and [4 + 2 − 1] annulations.[6] These processes proceed through either ionic or radical intermediates in multistep or single-step operations. Among the most recent reports are the anionic annulations of Beak,[3a,j] the radical annulation of Feldman,[3b] and the interesting atom-extrusion modulated approach of Larsen.[6b] Over the last 10 years, we have developed a [4 + 1]-annulation protocol based on the intramolecular cyclopropanation of dienes and the subsequent rearrangement of the resulting vinylcyclopropanes to annulated cyclopentenes.[7] This approach provided a reliable technology for the total synthesis of triquinane sesquiterpenes, and its extrapolation to nitrogen-[8] and oxygen-containing[9] analogues furnished pyrroline and dihydrofuran annulations via the rearrangement of vinylaziridines and vinyloxiranes, respectively. Upon close inspection of the retrosynthetic analysis involving the [4 + 1] annulation (i.e., 1,2 disconnection, Figure 1), it became clear that the parent target system of this approach, diquinane **1**, may be disconnected in an additional mode to provide a system composed of an enone and synthon **4**. Both **2** and **4** represent either carbenoids or enolate anions equipped with incipient leaving groups such as halides. In both instances, the retrosynthetic transition states leading to **1** involve the net participation of six π-electrons and are interconvertible without the movement of participating atoms.[10] The two projected synthons, namely **2** versus **3** and **4**, are therefore related through resonance-type arguments.[11] Synthetically, the equivalent of **2** becomes a diazo ketone, and the equivalent of **4** is the known reagent **5** utilized in bisannulation protocols of Hagiwara.[12] The interaction of reagent **5** with carbonyl compounds can be interpreted as either a vinylogous Darzen reaction[12c] or vinylogous McCoy reaction,[13] since the formation of epoxides or cyclopropanes by use of α-chloro esters[14] or α-chloro sulfones[15] as well as α-chloro imines[16] is well established.[17]

In this manuscript, we examine the experimental parameters governing the addition of the dienolate anions of **5** and of its more highly substituted derivatives such as **6** and **7** to enones to produce vinylcyclopropanes of type **8**, Figure 2.[18] The question of pK_a differences between the carbon- and the oxygen-functionalized substrates of type **5** and **6**, as well as the effect of such substituents on the regioselectivity of addition of the resulting dienolates to carbonyls, is addressed in detail.

The control of the rearrangement pathways of vinylcyclopropanes of type **8** to either diquinane **1** or bicyclo[3.2.1]octane **9** is also examined. These processes are [2 + 3][18] and [3 + 4][19] annulation equivalents respectively for the union of enones with **5**, Figure 2. The utility of this topological selectivity in the

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(10) This unique feature requires arguments in topology and molecular graph complexity. For a discussion of such concepts, see: Turro, N. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 882. And: Bertz, S. H. *J. Am. Chem. Soc.* **1981**, *103*, 3599. See also ref 7a and 21.

(11) We would like to propose the term "system resonance" or "retrosynthetic resonance" to express the use of this terminology in evaluating various elements of synthetic design.

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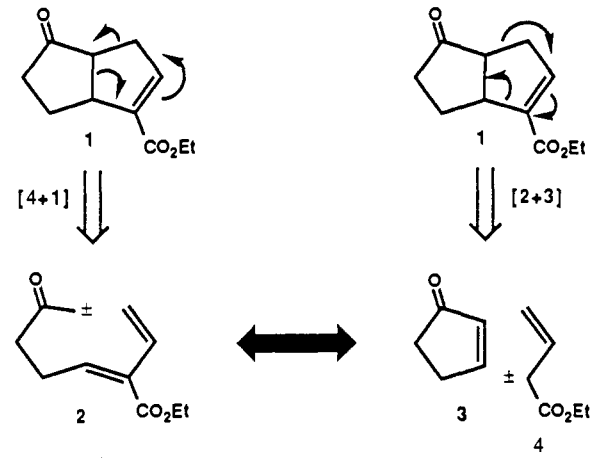

Figure 1. [4 + 1] and [2 + 3] disconnections in cyclopentene annulations.

production of fused or bridged systems is explored. The application of the [2 + 3]-annulation protocol to a short synthesis of retigeranic acid (**11**) from the highly substituted α-bromocrotonate ester **10** highlights the discussion of this methodology.[20]

Results and Discussion

Following the preliminary disclosures[18] on the additions of Hagiwara's reagent to carbonyl substrates, we focused on the investigation of, first, the stereochemistry of the vinylcyclopropanation and, second, the rearrangement pathways of vinylcyclopropanes of type **8** to bridged systems such as **9** via the Cope rearrangement.[19] A complete mechanistic analysis of the interaction of dienolate anion **5c** with enones is depicted in Figure 3 for the case of 2-cyclopentenone.

An interesting control of both the topography and topology[21] of the annulated ring systems can be realized from the analysis of the pathway of this reaction. The initially formed kinetic addition product **12a** will immediately collapse to vinylcyclopropane **8** if the alignment of the bromine is appropriately antiperiplanar for such a displacement. In case of improper alignment, there may be sufficient time for enolate equilibration to **12e** and the vinylogous displacement of bromine from **12e** to **9**. Another alternative would be the S_N2 displacement of bromine from **12e** to form cyclobutane **14**. The formation of enolate **8c** from either **8-exo** and **8-endo** and the subsequent Cope rearrangements would lead to **9** as well. The relationship between **1**, **9**, and **14** is a topological[21] one, whereas the relationship between **1** and **13** is topographical[21] and can be controlled by differential cleavage of bonds a and b in cyclopropanes **8**. Whereas this type of regiochemistry is easily controlled in the rearrangements of vinylaziridines[8,22] and vinyloxiranes,[9,23] cyclopentenes **8** do not possess activation of bond b unless an electron-donating group (X) is present. In such a case, nucleophilic opening/reclosure would lead to **1**, whereas thermolysis would lead to **13**.

Vinylcyclopropanation of Enones. The addition of the lithium dienolate of **5**, reagent **5c**, produced vinylcyclopropanes in good to excellent yields (Table I). The vinylcyclopropanes were obtained as mixtures of exo/endo isomers with respect to the vinyl group in nearly statistical ratios. The effects of the counterion and the leaving group were briefly addressed, but these were shown not to have a pronounced effect on the stereochemistry of the cyclopropanes.[18] Surprisingly little information is available on the stereospecific interaction of ester dienolates with enones. Among the first examples of such a process are Oppolzer's khusimone synthesis[24] and the investigations of the reaction of the vinylogous Reformatsky reagents with enones.[25] Heathcock's model for the determination of the stereochemistry of Michael adducts from ester enolate additions to enones[26] would apply only if both *E* and *Z* dienolates were involved in the reaction. From other studies, we believed that the reacting species was the *E* dienolate only, based on the stereospecific preparation of only *syn*-vinyloxiranes from aldehydes.[9] However, in the vinylcyclopropanation reaction of enones under identical conditions, the exo/endo ratios of vinylcyclopropanes were random. Initially it appeared that perhaps the presence of bromine on the dienolate anion drastically altered the stereoelectronic requirements for the transition states, similar to Heathcock's propositions.[26] Furthermore, studies by Rathke[29] and Schlessinger[30] on ester dienolate anion formation, by Saunders[32] on LDA deprotonation of carbonyl compounds, and by us[27,28,33] led us to assume that crotonate dienolates may prefer the closed form **5c**. Whatever the reacting species, it was found to be formed from either **5a**, **5b**, or a mixture of the two regardless of the presence or absence of HMPA in the reaction mixture. As the stereospecific condensation of **5c** with aldehydes yielded only adducts with a syn relationship between the hydrogen and carbethoxy substituents, the steric integrity of the reacting dienolate could be invoked as an explanation.[9]

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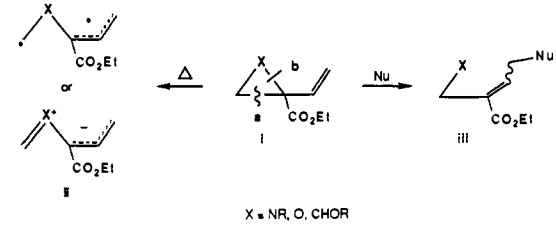
(22) The control of regiochemistry in vinyl-substituted three-membered rings is easier with nitrogen and oxygen cases because different reaction intermediates are involved following the cleavage of the three-membered ring. Thermolysis is believed to proceed through ylide or radical intermediates of type ii generated upon cleavage of bond a, whereas the nucleophilic opening requires deposition of the net charge on atom X with the cleavage of bond b. In ketocyclopropane, only bond b is activated toward either type of cleavage.



(23) The nucleophilic opening of vinyloxiranes cannot be controlled. Only the use of SmI_2 led to stereoselective ring opening, with nucleophilic attack always occurring β to the ester.

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(28) The stereochemistry of the dienolates was determined by ^{13}C and ^{1}H NMR of the silyl ketene acetals and by low-temperature ^{13}C and ^{1}H NMR of the lithium dienolate anions in THF-d_8. As of this writing, it appears that both *E* and *Z* dienolate anions are generated, but there is a rapid equilibration to one reacting species in those reactions that are stereospecific. Details of this work will be published elsewhere.

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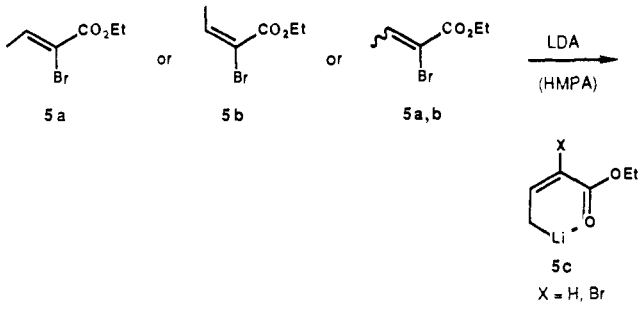
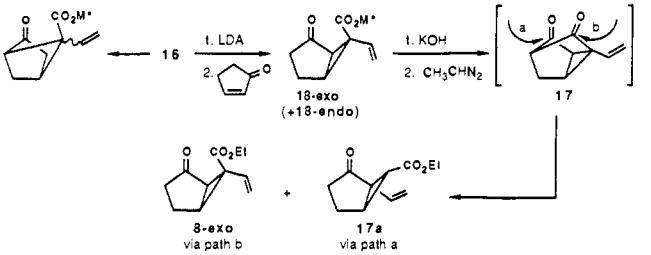
(33) The *E* geometry of **5c** was deduced by comparisons to the dienolates of ethyl crotonate.



There are four possible transition states, **15a–d**, for the approach of **5c** to enones. Of these only two, **15a** and **15c**, lead to initial Michael-type adducts, namely **12a** and **12c**, which require no bond rotation for their collapse to cyclopropanes **8-exo** and **8-endo** in the exo and endo configurations, respectively. The other two, **15b** and **15d**, form bromo esters **12b** and **12d**, which must rotate prior to displacement of the bromide to yield again **8-exo** and **8-endo**, respectively. Heathcock has shown that the geometry of simple ester enolate anions determines the stereochemistry of the initial Michael adduct with acyclic enones.[26] However, this model appears to fail for dienolate anions, especially if the closed form **5c** is invoked as the reacting species, as there may be little drive toward the intramolecular complexation of lithium to the enone oxygen. While such complexation has been invoked in the eight-membered transition state proposed by Heathcock for acyclic enones, only transition state **15c** is, in principle, capable of a similar process. As the size of the ester group increases, initial transition states **15a** and **15d** would be disfavored. Of the intermediate bromides **12b** and **12c**, originating in the more favorable transition states **15b** and **15c**, only **12c** is set for internal cyclopropane formation. The rotation in **12b** or **12c** would be disfavored; hence, time would become available for isomerization of the respective enolate anions and the eventual displacements to stereoisomers of **14**. Such a phenomenon was expected to account for the formation of cyclobutanes such as **14** during the additions of **16**[34] to cyclopentenone, although we have not observed this to date.[34,35] Table I shows several vinylcyclopropanes prepared as mixtures of exo/endo isomers from various enones in excellent yields. The exo/endo ratios were determined by structural assignment, which depends on the analysis of the chemical shifts (^{1}H and ^{13}C) associated with the cyclopropane ring protons, as these are shielded by either the vinyl or carboxyl groups. The initially reported procedure[18] for this reaction had to be adjusted to avoid lower yields resulting from anionic polymerization of **5c**.[9,36] This problem was avoided by careful control of the reaction parameters such as temperature, concentration, time, and modes of reagent additions; these results have been reported.[9] The optimum conditions involved generation of the dienolate anions of α-bromocrotonates and addition of the enones at −100 °C followed by quenching at low temperatures. This statement applies only to dienolates derived from **5** and **6**. The more highly substituted crotonates such as **24**, **16**, and **10** showed regioselective deprotonation and readily formed the corresponding vinylcyclopropanes in good yields. Little proton abstraction occurred at −100 °C, so these dienolates were formed at −78 °C. In the case of the silylated crotonate **6**, some polymerization of the dienolate took place even at −100 °C. The possibility of a γ-localized anion participating in a Brook-type equilibrium cannot be ruled out at this point. We are still optimizing the conditions of this reaction to see how this polymerization can be avoided. The more substituted crotonates showed a more subdued tendency toward enolization. The oxygenated crotonate **7** was also deprotonated with LDA in THF/HMPA at −78 °C, when it was discovered that at −100 °C the proton abstraction was too slow and self-condensation interferred.

The stereoisomers of the vinylcyclopropanes **8**, **18**, **19**, **20**, **25–28**, **30**, and **31** were separated for full spectral characterization. Each set of the two isomers converged at the stage of the corresponding cyclopentene upon pyrolysis so that no separation was required in preparative experiments. Surprisingly, all of the vinylcyclopropanes **19**, **20**, and **28**, containing an enol ether moiety as the vinyl group, were obtained as single isomers with respect to the enol ether double bond. In the case of menthyl ester **16**, the aforementioned analysis of the course of the reaction was not borne out: cyclobutane **14** was not isolated but was thought to be present in the final reaction mixtures obtained by base-catalyzed hydrolysis and diazomethane treatment of **18-exo**. Apparently during the hydrolysis of **18-exo**, diketone **17** was produced, which then underwent cleavage to two regioisomeric acids. Their esters were



isolated and identified as **8-exo** (path b) and **17a** (path a). The isolation of **17a** led to the initial erroneous assignment as **14**. Subsequent transesterification of these compounds to their ethyl esters and their analysis by a chiral shift study revealed only 5% ee. (See comment in ref 44.) The projected asymmetric induction in this particular series did not come to fruition. We were more successful in obtaining enantiocontrol through utilization of a chiral enone. The condensation of the dienolates of **5** and **6** with chiral enone **22** produced the corresponding vinylcyclopropanes with complete diastereofacial selectivity. The cyclopentene annulated product, **38**, is a crucial intermediate in our approach to (−)-specionin.

[2 + 3] Annulations: Thermolytic Rearrangements. The vinylcyclopropanes listed in Table I were subjected flash vacuum pyrolysis over a $PbCO_3$-conditioned surface[37] to furnish cyclopentene annulated systems **1**, **32–34**, **37**, **38**, and **40**. In some instances, the competing processes that are well documented for these processes[38] provided enones **36a** and **36b** as minor con-

36a **36b**

stituents.[39] We discovered that this reaction pathway could be

(34) Hudlicky, T.; Radesca, L.; Rigby, H. L. *J. Org. Chem.* **1987**, *52*, 4397.

(35) The regioisomeric vinylcyclopropane **17a** was initially incorrectly assigned the structure **14** based on the interpretation of its ^{1}H and ^{13}C NMR spectra.

(36) The dienolate of 2-bromocrotonate polymerizes at temperatures above −90 °C. The dienolate of **6** polymerizes even more readily: at −100 °C, substantial polymerization occurs. Since we are limited by the freezing point of THF, we are currently exploring other methods for controlling this polymerization. With the dienolate of **7**, two competing processes must be balanced. At lower temperatures (below −90 °C), polymerization can be avoided. However, due to the decreased acidity of the γ-protons, enolization is too slow at this temperature, and self-condensation becomes a problem. The best "compromise" temperature is −78 °C. At this temperature, self-condensation is minor and polymerization not too great.

(37) This conditioning is necessary, as pointed out in detail in previous publications (ref 7). The use of $PbCO_3$-coated glass was incorporated as the best approximation to the pyrolyses of ketovinylcyclopropanes over lead–potash glass, which is unfortunately no longer available thanks to the EPA. For the original reference on its use, see: Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265.

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(39) No detailed temperature profile was done to optimize enone formation, although one should expect this product to predominate at temperatures around 400 °C.

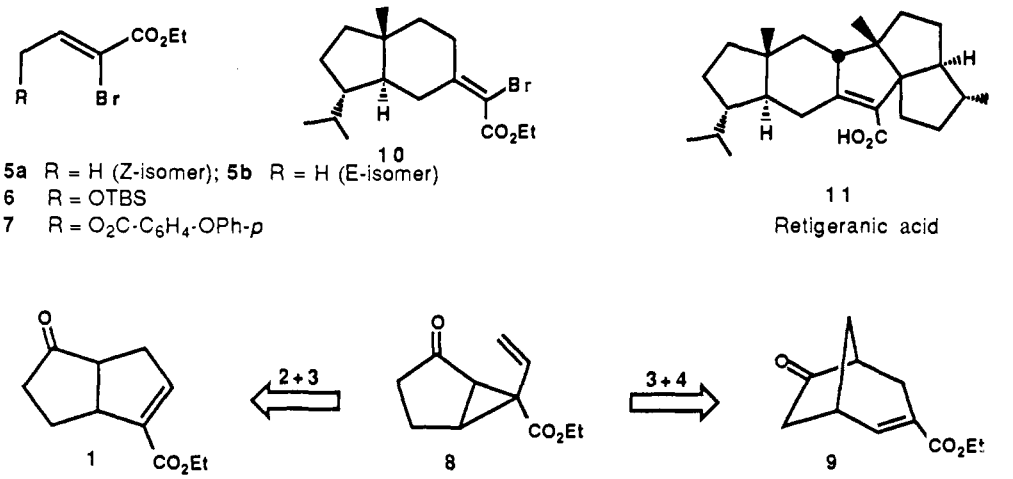


Figure 2. Rearrangement pathways for vinylcyclopropanes derived from enones.

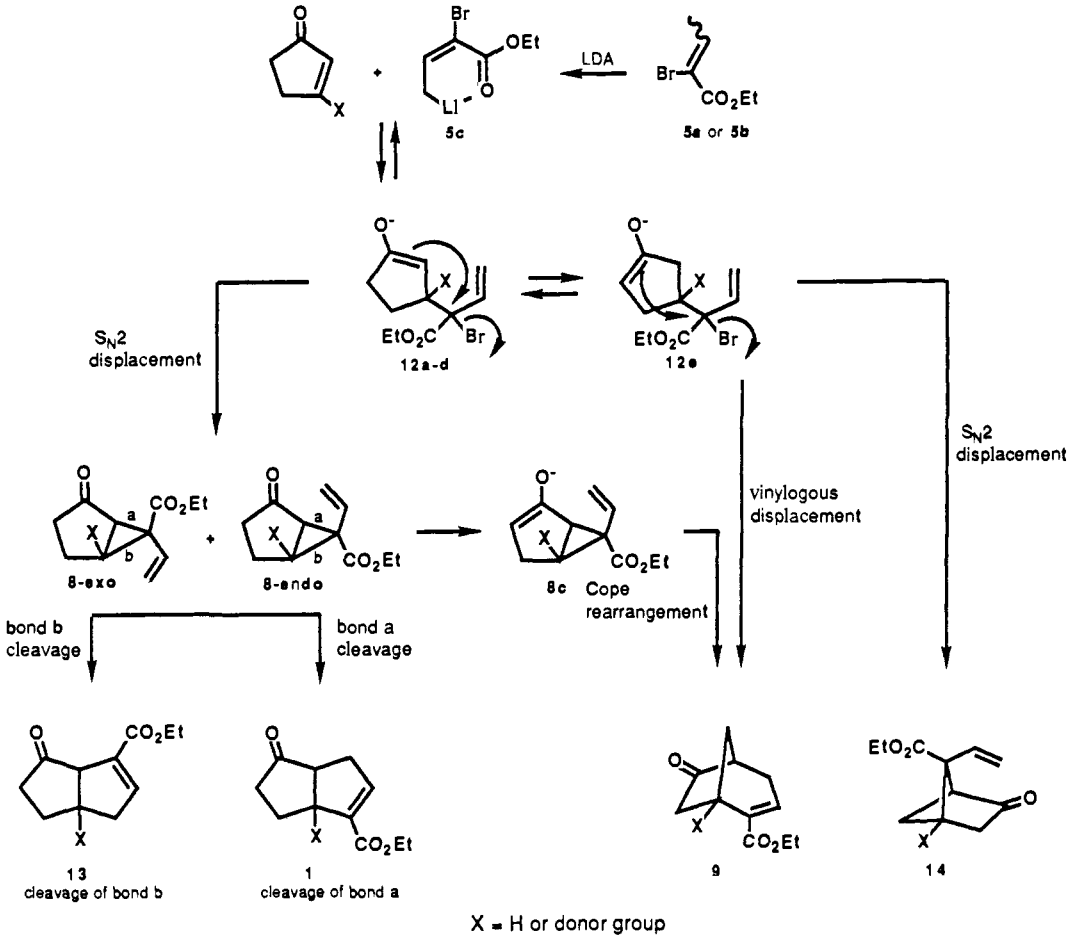


Figure 3. Mechanistic pathways for the addition of **5c** to enones.

suppressed by increasing the temperature of the pyrolysis (Table II). The formation of enones of this type has been observed in cases where substitution of the vinylcyclopropane does not unambiguously rule out the competing cleaveage of the bond situated β to the carbonyl.[7a,c] Although **36a** and **36b** could in principle arise by diradical cleavage followed by hydrogen abstraction, the isolation of single isomers (*E*) of these enones supports a concerted homo [1,5]-sigmatropic shift pathway followed by conjugation of the double bond.[7a,b,38c,d] The temperature dependence of the product profile is shown in Table II and is in agreement with previous results supporting the reversibility of the retro-ene process at lower temperatures.[38d] At lower temperatures (500 °C), enone **36a** was formed in 42% yield. However, at higher temperatures (550 °C), diquinane **1** was the exclusive product. Similarly, in the case of **25-exo** the same trend was observed. Enone **36b** was present in 31% yield at 575 °C, but at higher temperatures (600 °C), only the cyclopentene annulated product **32** was detected. Only the exo isomer was in each case subjected to this optimization procedure. The pyrolysis of **26** furnished the perhydroazulene skeleton **33**, which we believe to be cis fused. The preparation of this compound via its vinylcyclopropane **26** proved particularly useful, as we have shown that intramolecular cyclopropanations of dienes by keto carbenoids did not lead reproducibly to closures of seven-membered rings.[40] The oxygenated cyclopropanes **20** and **28** gave the corresponding cyclopentenes **34** and **38** exclusively

(40) Hudlicky, T.; Sheth, J. P.; Gee, V.; Barnvos, D. *Tetrahedron Lett.* **1979**, 4889.

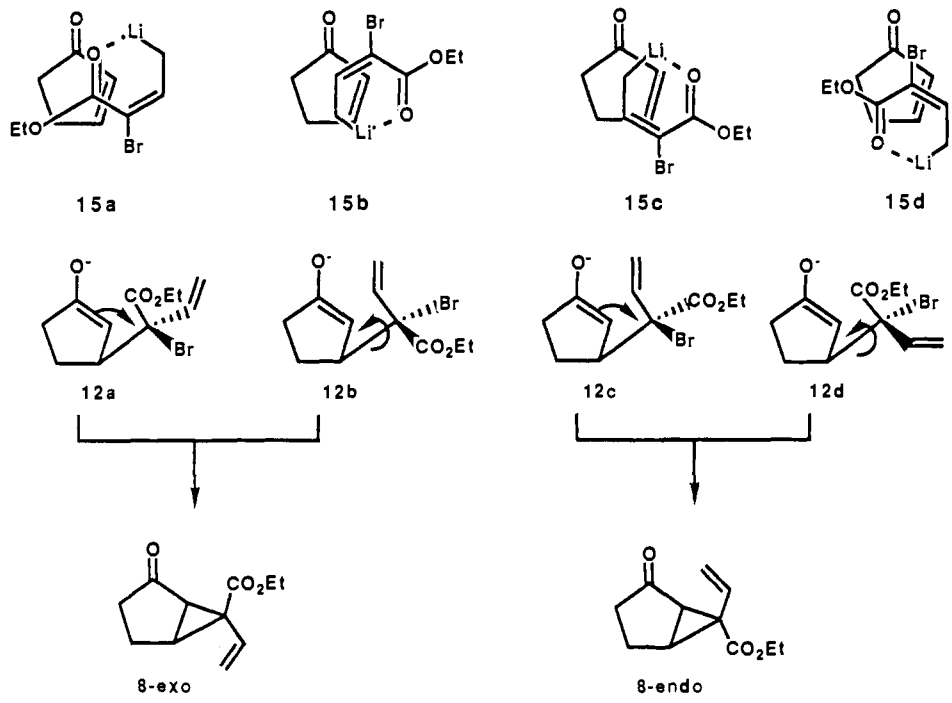
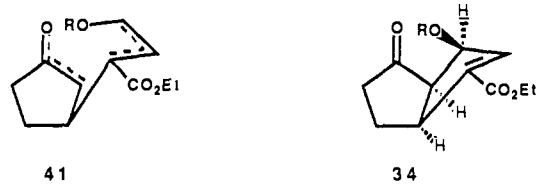


Figure 4. Analysis of the transition states for vinylcyclopropanation.

as their endo isomers, in analogy with the documented endo effect observed for closures of species such as **41**.[41,42] Vinylcyclopropane



19 gave predominantly diquinane **35-endo** (endo:exo = 72:28). The low yield in the preparation of **34** can be attributed to the difficulty encountered in evaporating the relatively high molecular weight vinylcyclopropane **20** through the hot tube, as the more volatile silylated derivative **28** gave tricycle **38** in 75% yield. The use of chiral enones such as **22**[43] in the cyclopropanation scheme led, via the thermolytic rearrangement, to chiral diquinanes such as **37** and **38**. This process serves quite well in incorporating the elements of enantiocontrol into this methodology, especially since poor results were obtained during the initial attempts at direct asymmetric induction with menthyl ester **16**.[44] Finally, vinylcyclopropane **31** furnished pentacyclic intermediate **40** (see the section on retigeranic acid for details) in what may be the limit of this particular technique. As the pyrolysis of **20** indicated, for hydrocarbons of molecular weight of greater than 400 or compounds containing more than four heteroatoms, other means of rearrangement may need to be found, as such compounds will not readily volatilize even under diffusion pump vacuum (10^{-4}–10^{-6} mmHg).

[2 + 3] Annulation: Nucleophilic Openings.[19] The thermolytic rearrangments provided cyclopentene annulated products in good yields. In practical applications, there is a natural limit to this

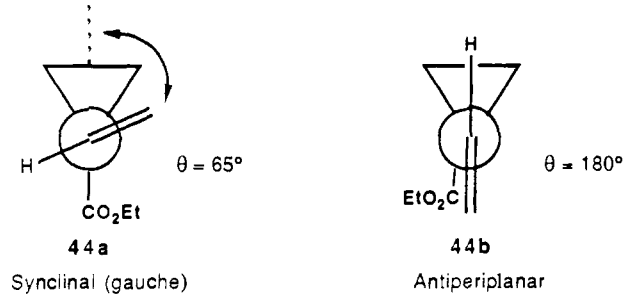


Figure 5. Conformation of vinylcyclopropane.

methodology, which is determined by the volatility of vinylcyclopropanes in high vacuum as well as by the interference of other chemical processes that would result from the presence of thermally sensitive functionalities. We therefore adapted the TMSI opening of cyclopropyl ketones developed by Miller[45] as the key step in this new annulation method (vide infra) (Table III). When vinylcyclopropanes **8-exo** and **8-endo** were exposed to TMSI, mixtures of allylic iodides **41** and **42** resulting from the vinylogous opening of the cyclopropane were obtained (Table III). The exo isomer of **8** gave only **41** and **42**, while **8-endo** yielded, in addition to the allylic iodides, products **9** and **43** (a ring-expanded product).[19] Similar nucleophilic openings by means of tosyl iodide were reported after the completion of this work.[46] Other vinylcyclopropanes gave more or less a random product distribution of allylic iodides, with one exception being the tricyclic precursors to pentalenene terpenes, which gave *Z* isomers only.[7,47]

(41) Wolff, S.; Agosta, W. C. *J. Chem. Res.* **1981**, 78.
(42) (a) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373.
(43) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735.
(44) In the preliminary communication regarding this work (ref 34), a level of asymmetric induction was reported as "good" and was based on a qualitative observation of the optical rotation. The chiral shift studies as well as the reexamination of the GC and NMR data have revealed low levels of induction (5% ee). The optical rotation observed initially was due to the contamination of the product by (−)-menthol.
(45) Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412.
(46) de C. Alpoim, M. C. M.; Morris, A. D.; Motherwell, W. B.; O'Shea, D. M. *Tetrahedron Lett.* **1988**, *29*, 4137.
(47) The following vinylcyclopropanes were cleaved stereoselectively (see ref 7c).

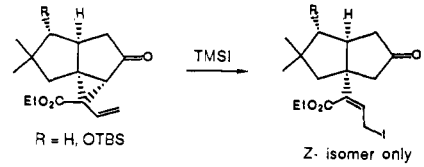
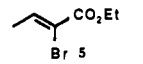
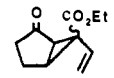
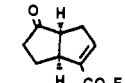
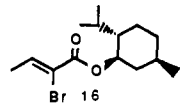
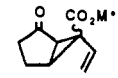
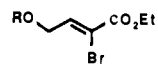
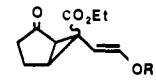
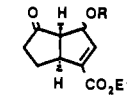
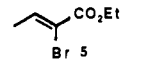
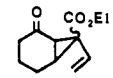
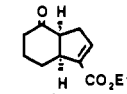
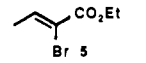
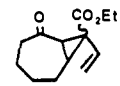
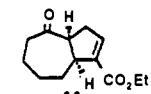
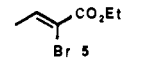
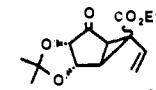
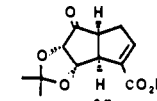
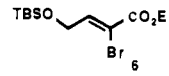
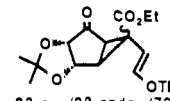
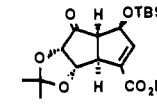
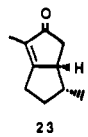
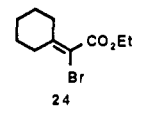
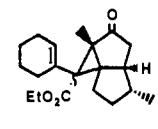
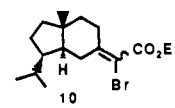
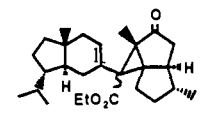
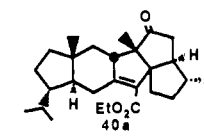


Table I. [2 + 3] Annulation of Enones

enone	bromocrotonate	vinylcyclopropane	cyclopentene
	 Br 5	 8-exo/8-endo (57/43) (67)[a] (98)[b]	 1 (43)[a] (550°)[d]
	 Br 16	 18-endo/18-exo (60/40) (80)[e]	SM (550°)[d]
	 6, R=TBS 7, R=CO(C$_6$H$_4$)OPh-*p*	 19-exo/19-endo (44/56) (38)[a] (65)[b] 20- exo/20-endo (70/30) (40)[a] (78)[b]	 35 endo/exo (72/28) (52)[a] (525°)[d] 34 endo/exo (99/1) (28)[a] (525°)[d]
	 Br 5	 25-exo/25-endo (68/32) (90)[a] (93)[b]	 32 (19)[a] (600°)[d]
 21	 Br 5	 26-exo/26-endo (63/37) (83)[a] (84)[b]	 33 (21)[a] (600°)[d]
 22	 Br 5	 27-exo/27-endo (66/34) (72)[a] (97)[b]	 37 (51)[a] (550°)[d]
	 Br 6	 28-exo/28-endo (72/28) (36)[a] (46)[b]	 38 (75)[a] (525°)[d]
 23	 24	 30-exo/30-endo (18/82) (40)[a]	—
	 10	 31-exo/32-endo (40/60) (56)[a] (79)[b]	 40a + 40b 1:1 (50)[a] (74)[b] (585°)[d]

When $TiCl_4$ was used in conjunction with TMSI, the stereoselectivity was improved up to an 80/20 ratio of *E*/*Z* iodides **41**/**42**. A detailed study was performed with cyclopentane cases **8** only. Changes in the reaction temperature did not lead to changes in product ratios, which might be expected based on changes in the conformer population in the two conformations depicted as **44a** and **44b**. Although conformation **44b** should be more stable with unsubstituted vinylcyclopropanes, synclinal arrangement **44a** would explain the predominance of the *E* isomer upon the nucleophilic opening and the increase in this isomer ratio upon the addition of Lewis acids (Figure 5). We reasoned that the bulk of the Lewis acid complexed to either carbonyl forced the vinyl group into the appropriate synclinal conformation **44a** at the time of the opening. Whereas we did not pursue this notion in detail, it appears that the bulk of the ester group itself could accomplish the same result. As both *E* and *Z* allylic iodides were obtained from both *exo*- and *endo*-vinylcyclopropanes, it became evident that the best solution to this problem would lie in the establishment of conditions that

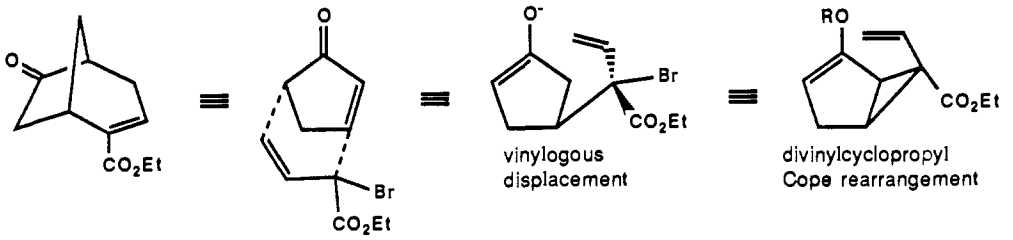
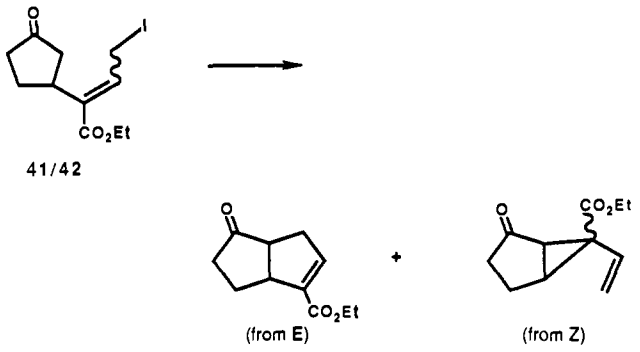


Figure 6. Synthon representation of the [3 + 4]-annulation methodology.

Table II. Temperature Dependence of Product Distribution

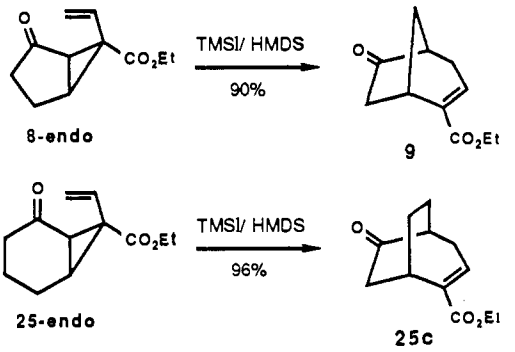
vinylcyclopropane	temp, °C			
8-endo	500	47	42	11
8-endo	550	98	2	0
silyl enol ether of **8-exo**	550	48	0	52
25-exo	575	69	31	0
25-exo	600	100	0	0

would "recycle" the wrong stereoisomer via reclosure to the vinylcyclopropane in analogy with a completely quantitative isomerization of *exo/endo*-vinylaziridines to annulated pyrrolines.[8c,49] Thus, the mixtures of iodides **41** and **42** were quenched at low



temperature with quaternary ammonium hydroxide in DMF/water. This led to the isolation of annulated cyclopentenes and starting vinylcyclopropanes in ratios identical with those of the *E/Z* iodides, respectively (determined by NMR).[48] Unlike the case of vinylaziridines where the initial silylated amine is nucleophilic enough to displace the iodide, leading to a mixture of the product and the starting material and eventually recycling of the entire mixture to annulated pyrrolines,[49] the enol ethers of **41/42** are, prior to the aqueous quench, not nucleophilic enough to accomplish such in situ recycling. The complete solution to this problem therefore lies in the development of a nucleophilic reagent whose hard–soft symmetry is such that it affords a ring-opened allylic iodide while generating an enol derivative nucleophilic enough for its displacement.[50,51] While the detailed investigation of the stereochemical control of the vinylcyclopropane opening forms the basis of our current research, we were, for the moment, satisfied with the present results, which bode well for a mild alternative to thermolytic rearrangements.

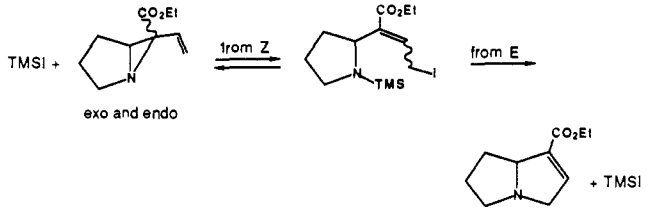
[3 + 4] Annulation. The silyl enol derivatives of vinylcyclopropanes of type **8** were transformed to the products of a divinylcyclopropane Cope rearrangement, with the carbonyl group in **8** serving as the latent functionality for generating the latent second vinyl group. All of the synthons depicted in Figure 6 are precursors of the target bicyclo[3.2.1]octane **9**, as outlined earlier in Figure 3. The generation of trimethylsilyl enol ethers from **8-endo** and **25-endo** took place at −20 °C with HMDS/TMSI.



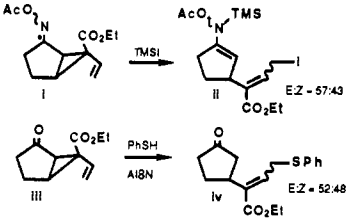
The intermediate enol ethers rearranged during warming to room temperature to **9** and **25c**, respectively. The corresponding enol ether derived from **8-exo** was thermally stable at room temperature and was isolated. Flash vacuum thermolysis yielded **9**, the product of the divinylcyclopropane Cope rearrangement,[52] and diquinane **1**. Subsequently, we discovered that the potassium salt of **8-endo** or **46-endo** rearranges at room temperature. This suggests a remote charge acceleration of the divinylcyclopropane Cope rearrangement.[53,54] The corresponding lithium enolate anion did

(48) The ratios of *E* to *Z* allylic iodides were determined by integration of the vinylic protons in the ^{1}H NMR spectrum. The vinylic proton of the *E* isomer appears as a triplet at 6.96 ppm, while that of the *Z* isomer appears at 6.11 ppm.

(49) The total "equilibration" in the opening of vinylaziridines proceeds as shown below:

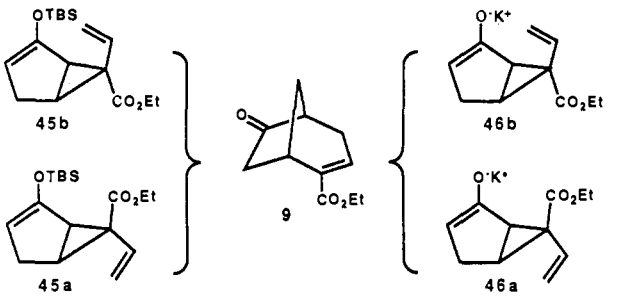


(50) Some of the conditions tested so far included the opening of the oxime i and the radical opening by thiophenol of ketone iii. No direct closures to cyclopentenes were observed during these reactions.

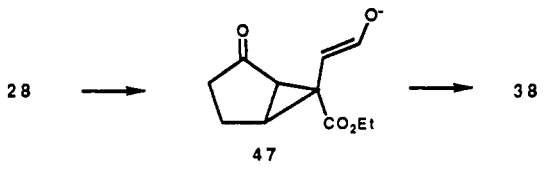


(51) The use of alkylboron bromides or tin iodides is being considered because of the appropriate hard–soft symmetry in the resulting enolate/counterion systems. The silylenol ethers obtained as intermediates simply are not nucleophilic enough to displace allylic iodides and therefore set up conditions similar to those encountered during the ring opening of vinylaziridines where the iodide displacement takes place through the agency of *N*-silylamine.[49]

(52) The exo isomers were previously thermolyzed at 500–550 °C. Substantially lower temperatures (180–220 °C) are necessary. For references to divinylcyclopropane Cope rearrangement, see: (a) Piers, E.; Ruediger, E. H. *J. Org. Chem.* **1980**, *45*, 1725. (b) Piers, E.; Jung, G. L.; Moss, N. *Tetrahedron Lett.* **1984**, *25*, 3959.



not undergo the rearrangement. The exo isomer did not rearrange or isomerize in refluxing THF or DME.[55] These results indicate that the divinylcyclopropyl Cope rearrangement may be subject to related anion-accelerated criteria through secondary orbital interaction like the oxyanion Cope process,[56] immonium ion accelerated Diels–Alder reaction,[57] enolate anion accelerated divinylcyclobutane rearrangement,[58] and other processes of this type.[59–61] Surprisingly, there are no prior examples of this process in the literature on divinylcyclopropyl rearrangements.[53] Most recently, the applications of this type of process to the aforementioned cyclopentene annulation through enolate anion accelerated reorganization of vinylcyclopropanes such as **28** via intermediate **47** have been realized.[62]

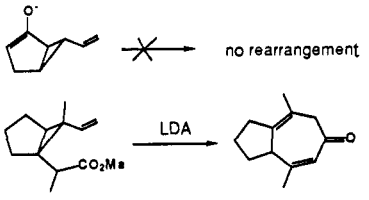


Total Synthesis of Retigeranic Acid. This unique compound isolated[63] over 20 years ago did not yield to chemical synthesis until 1985 when Corey prepared its racemate.[64] At this time, the existence of two isomers, retigeranic acid A (**11**) and retigeranic acid B (isomeric at C-9), was disclosed when it was discovered that the natural product contained both.[64] This was not anticipated, of course, by either the Hudlicky group or the Paquette group, whose approaches in 1980 and 1981, respectively, targeted **11** as the synthetic goals. Retigeranic acid is unique in several aspects. It was the first terpene isolated whose structure contained an angular triquinane; it has a pentacyclic structural array unlike any other sesterterpene isolated to date, and so far it possesses no known biological activity, although its parent genus, Himalayan lichen *Lobaria regigera*, contains known medicinal agents.[63,65a] Synthetic approaches to this compound have been limited and have yielded to date only four syntheses: Corey's,[64] Paquette's,[65] Wender's,[66] and ours.[20] The first documented approach to retigeranic acid was our initial attempt[67–69] following the convergent disconnection, shown in Figure 7, and formulated upon recognition that the two remote chiral centers in rings A and E could be set by using menthene and pulegone, respectively, as starting materials. The same solution to this chiral control was later incorporated by Paquette.[65,73] This approach relied on the construction

(53) To our knowledge, divinylcyclopropane Cope rearrangements accelerated by anions of this type have not been reported (see ref 54). However, Wender has shown that simple [3,3]-sigmatropic Cope rearrangements of 1,5-dienes are subject to acceleration by enolate anions remotely situated to the reaction center: Wender, P. A.; Ternansky, R. J.; Sieburth, S., McN. *Tetrahedron Lett.* **1985**, *26*, 4319.

(54) For discussion of charge accelleration, see: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

(55) In refluxing DME containing 18-crown-**6**, the exo isomer undergoes rearrangements other than Cope. The identity of the products is not known at this time. Aside from the discussion here, the unpublished efforts in this area by Piers and Heathcock are known to us:



(56) (a) Paquette, L. A.; DeRussy, D. T. *Tetrahedron* **1988**, *44*, 3139. (b) Paquette, L. A.; Crouse, G. D.; Sharina, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 4411. (c) Crouse, G. D.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 3167. (d) Evans, D. A.; Nelson, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 774. (e) Evans, D. A.; Golub, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(57) Jung, M. E.; Buszek, K. R. *J. Org. Chem.* **1985**, *50*, 5440.

(58) Majetich, G.; Hull, K. *Tetrahedron Lett.* **1988**, *29*, 2773.

(59) (a) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635; (b) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279; (c) Ireland, R. E.; Anderson, R. C.; Baboud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. (d) Ireland, R. E.; Vevert, J. P. *J. Org. Chem.* **1980**, *45*, 4249; *Can. J. Chem.* **1981**, *59*, 572. (e) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (f) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, 3975.

(60) Danheiser, R. L.; Martinez-Davila, C. M.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443. (b) Danheiser, R. L.; Martinez-Davila, C. M.; Morin, J. M., Jr. *J. Org. Chem.* **1980**, *45*, 1340.

(61) Dinnocenzo, J. P.; Conlon, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 2324.

(62) As of this writing, the transformation **28** to **38** has been accomplished. Hudlicky, T.; Heard, N.; Fleming, A. *J. Am. Chem. Soc.*, in preparation.

(63) Rao, P. S.; Sarma, K. G.; Seshadri, T. R. *Curr. Sci.* **1965**, *34*, 9; **1966**, *35*, 147. Kaneda, M.; Takahashi, R.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.* **1972**, 4609.

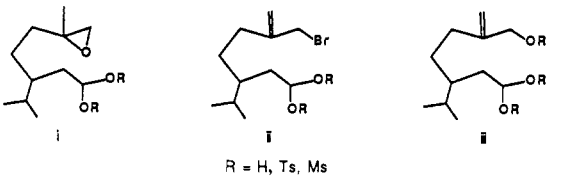
(64) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339. The correct X-ray structural assignment was due to one of the isomers (retigeranic acid A) crystallizing as an anilide in the pure state.

(65) (a) Paquette, L. A.; Wright, J.; Drtina, G. J.; Roberts, R. A. *J. Org. Chem.* **1987**, *52*, 2960; *J. Am. Chem. Soc.* **1988**, *110*, 5806. (b) Paquette reported his MM2 results as a 2.4-kcal difference in stability of pentacycles **62**. He also made a comment about the misalignment by 40° of the allylic H at C-5b with the orbitals of the acrylate in **62**, thus precluding its kinetic acidity.

(66) Wender, P. A., private communication. The Stanford synthesis was completed in late 1987.

(67) Presented in part at the ACS Central and Great Lakes Regional Meeting, Dayton, OH, May 1981; Abstract 273.

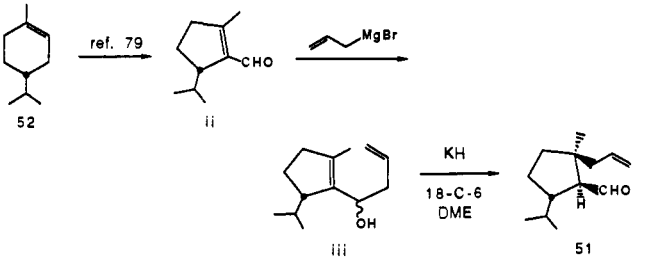
(68) The aldehdye **49** was prepared, along with derivatives i–iii. These reagents were used in attempts at γ-alkylation of **48**, which proved to be unsuccessful.



(69) Hudlicky, T.; Short, R. P. *J. Org. Chem.* **1982**, *47*, 1522.

(70) During our research in 1981 on the union of **48** and **49**, a variety of acyl anion equivalents derived from **49** failed to add the acrylate unit in **48**. In retrospect, this was probably due to the lack of orbital overlap between the olefin and the carbonyl in **48**.

(71) Aldehyde **51** was prepared as shown. We are grateful to Ramon Tubio of the Universidad de la Republica, Montevideo, Uruguay, for carrying out this work under the sponsorship of the Fulbright Foundation (research and travel fellowships to Ramon Tubio).



(72) The stereochemistry of **51** was established by chiral shift studies on the aldehyde and its alcohol. The aldehyde was also converted to enone i by $PdCl_2/O_2$ followed by aldol condensation. The stereochemistry of i was assigned by ^1H NMR.

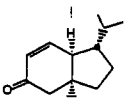


Table III. TMSI Openings of Vinylcyclopropyl Ketones

vinylcyclopropane	nucleophile	41	42	43	9
8-endo	TMSI	19	21	42	18
8-exo	TMSI	40	60	0	0
25-endo	TMSI	46	32	22	0
25-exo	TMSI	55	27	18	0
8-exo	$TMSI/TiCl_4$	20	80	0	0
25-exo	$TMSI/TiCl_4$	25	75	0	0

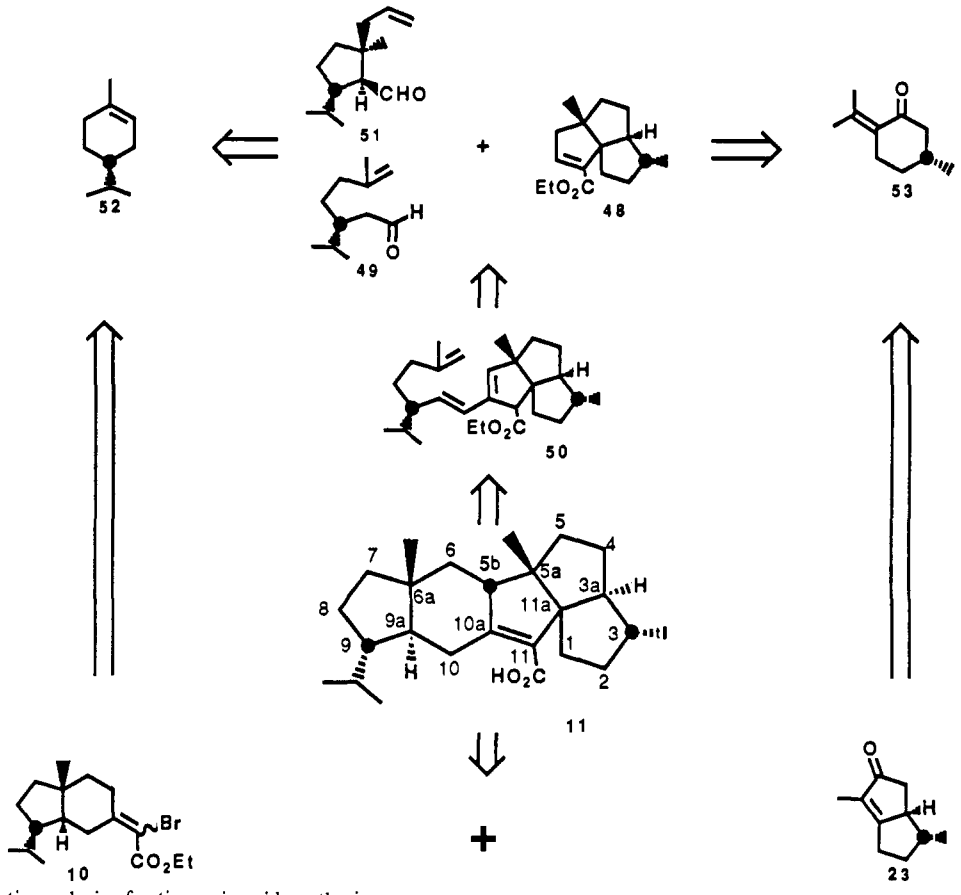


Figure 7. Retrosynthetic analysis of retigeranic acid synthesis.

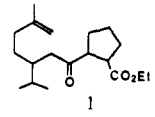
of appropriate right and left synthons, **48**[69] and **49**, and their union to the Diels–Alder precursor **50**. The triquinane **48** has been synthesized,[69] but all attempts at its union with **49** and further elaboration to **50** failed.[70] The Diels–Alder approach was subsequently successfully employed by Wender, who produced the requisite right half using the meta photocycloaddition protocol.[66]

Our second approach, also unfruitful, relied on the combination of a premade ring A fragment, **51**, with the acrylate **48**, but this was abandoned upon the discovery that the precursor to **51** was generated with the wrong stereochemistry.[71,72] At about the same time, Paquette's strategy, relying on the union of a similar fragment with a tricyclic enone, became known[73] and with it the experimental grievances surrounding any bond-forming sequences leading to the substituted central cyclopentene **11**. Our final approach utilized the [2 + 3]-annulation protocol, the union of crotonate **10** with enone **23** to arrive at a short completely enantiocontrolled synthesis of **11**.[20] All of the approaches, including our last one, share one problem in common. The bond-forming schemes and the regio- as well as the stereochemistry of carbons adjacent to the acrylate function of **11** all proved problematic and revealed the astonishing inability of modern chemical theory to predict or anticipate such problems.[74] In his full paper, Paquette addressed the equilibrium at C-5b in **11**, and in this manuscript, we report a solution to this anomaly. Thus, in addition to all the curiosities associated with retigeranic acid, another one needs to be added: synthetic unpredictabilities connected to the operations on the central cyclopentanoid ring which, as will be revealed below, has peculiar stereoelectronics associated with it and any of its latent synthons.[74,75]

In order to test the [2 + 3] approach on a simple model, bromo ester **24**[76] was prepared and condensed with enone **23**[77] to generate

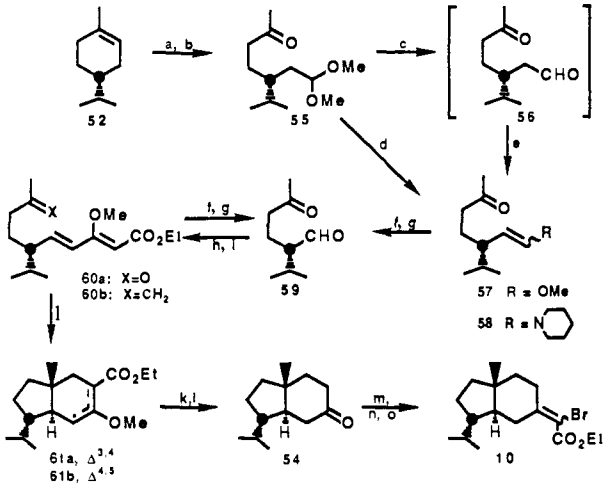
(73) Paquette, L. A.; Han, Y.-K. *J. Org. Chem.* **1979**, *44*, 4014; *J. Am. Chem. Soc.* **1981**, *103*, 1835.

(74) An example of the unpredictable behavior of strained acrylates of type **48** is exemplified by the successful preparation of i from **49** and ethyl cyclopentenecarboxylate using acyl anion equivalents. The same reaction failed with **48**.



i

(75) Additions to **48** of such reagents as bromine and hydrogen peroxide uniformly failed.



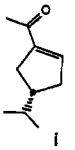
Reagents: a) O_3, MeOH-CH_2Cl_2; b) Me_2S, p-TsOH; c) 3% aq $HClO_4$, THF; d) $KHSO_4$; e) Piperidine, Et_2O; f) O_3, MeOH-CH_2Cl_2; g) Me_2S;)h $(MeO)_2P(O)CH_2C(OMe)CHCO_2Et$, LDA, HMPA, THF; i) $\phi_3P^+CH_3Br^-$, n-BuLi, THF; j) Toluene, Δ; k) HCl, THF; l)LiI, DMF; m) $Me_3SiCH_2CO_2Et$, LDA, THF; n) Br_2, CCl_4; o) DBU, DME

Figure 8. Synthesis of the left-hand portion.

an exo/endo mixture of vinylcyclopropanes **31**. (See Table I.) This was a good indication that α-bromocrotonates substituted at the γ-position would subscribe to the same regiochemical mode of addition as the simple crotonate **5**. The synthesis of a bromo ester **10**, outlined in Figure 8, utilized the known ketone **54**, which has been prepared by both Fallis[78] and Corey[64] in the racemic form. Menthene (prepared by partial hydrogenation of limonene)[79] was ozonized and trapped as ketoacetal **55**, as this compound was stable to distillation and prolonged storage, whereas the direct ozonolysis product, ketoaldehyde **56**, polymerized easily.[79,80] The aldehyde was easily regenerated as needed by mild hydrolysis of **55** with 3% $HClO_4/THF/H_2O$.[80] Conversion of these materials to the chiral form of Fallis's intermediate, *nor*-aldehyde **59**, was accomplished in several ways and initially proved troublesome. Enol ether formation from **56** or **55** was irreproducible,[81] whereas enamine preparation was reliable.[79] Conversely, the ozonolysis of **57**[82] cleanly gave **59**, whereas the ozonolysis of **58** was complicated, especially with respect to product purification, by the presence of oxidation products of *N*-formylpiperidine. This obstacle was finally surmounted by reproducible generation of **57** using a published procedure[83] in about 50% yield.[84]

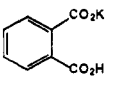
Ketodiene **60a** was prepared by Horner–Emmons olefination of **59**, with the phosphonate ester derived from 4-bromo-3-methoxycrotonate.[78,85] Methylenation of the ketone carbonyl in **60a** provided **60b** in 80% yield. To ensure that no racemization had taken place, we ozonized a sample of this material back to ketoaldehyde **59** and found that the rotation of this product was identical with that of the freshly prepared material, indicating that no base-catalyzed racemization occurred during the two Wittig processes. Triene **60b** was converted to ketone **54** by using the procedure of Fallis.[78] In this light, it should be mentioned that the Diels–Alder reaction to yield the mixture of conjugated and deconjugated enol ethers **61** has been shown to be troublesome and is probably an equilibrium process.[86] In dichlorobenzene, Fallis obtained high yields of **61**, but the procedure failed with a "fresh" bottle of solvent.[87] In toluene, yields were consistently 25–30%, with the remainder of the mixture being starting material, which was recycled. In "wet" dichlorobenzene, the yields were higher[88] because the intermediate enol ethers were hydrolyzed and decarboxylated to **54**, thus removing them from participation in a retro-Diels–Alder process. Unfortunately, any unreacted starting material was destroyed in these reactions by hydrolysis. Higher temperatures did not improve the ratio of starting material to product and began to give the cis-fused isomer of **61** as a contaminant.[89] High-pressure or flash vacuum pyrolysis did not lead to marked improvements in the yield of **61**.[90] Thus, recycling of unreacted triene **60b** proved to be the most effective method for generating large quantities of **61**, which was cleanly hydrolyzed to **54** after separation from **60b** by flash chromatography.[91] The overall yield of **54** from triene **60b** was 58%. The overall yield of **54** from menthene was 23% (based on recovered starting material).

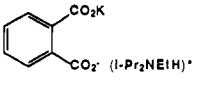
(76) Stacy, G. W.; Cleary, J. W.; Gortatowski, M. J. *J. Am. Chem. Soc.* **1957**, *79*, 1451.
(77) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690.
(78) Attach-Poku, S. K.; Chau, F.; Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1985**, *50*, 3418.
(79) White, J. D.; Ruppert, J. F.; Avery, M. A.; Torii, S.; Nokami, J. *J. Am. Chem. Soc.* **1981**, *103*, 1813.
(80) Hudlicky, T.; Short, R. P., unpublished observations.
(81) Distillation of neat ketoacetal **55** over *p*-TsOH did not provide any enol ethers. However, an old bottle of acetal **55** was contaminated with the *E* isomer of **57**, suggesting that such a conversion took place on standing. It was also distilled over diisopropylethylammonium tosylate, but enone i was the only product.



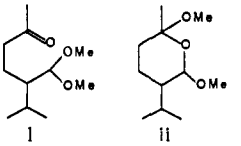
i

Other methods that were tried and failed involved stirring ketoacetal **55** with different catalysts (ii, iii, iv, or v) at 70–90 °C and 15 mmHg.

ii: $CH_3(CH_2)_{14}CO_2H$ / NaH (2:1) iii: 

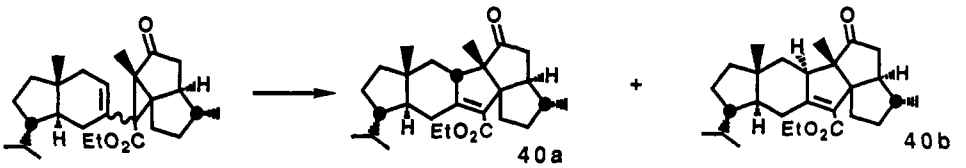
iv: $(CH_3(CH_2)_{14}CO_2)^-(i\text{-}Pr_2NEtH)^+$ v: 

(82) Ozonolysis of **57** had to be performed in acid-free MeOH. When spectroscopic grade MeOH was used, a mixture of acetals i and ii was obtained. This was undesired because recovery of **59** from these compounds in acidic medium would have been detrimental to the chiral center. It is interesting to note that stirring aldehyde **59** in MeOH in the presence of *p*-TsOH overnight did not yield acetal i, which was only obtained on workup of the ozonide.

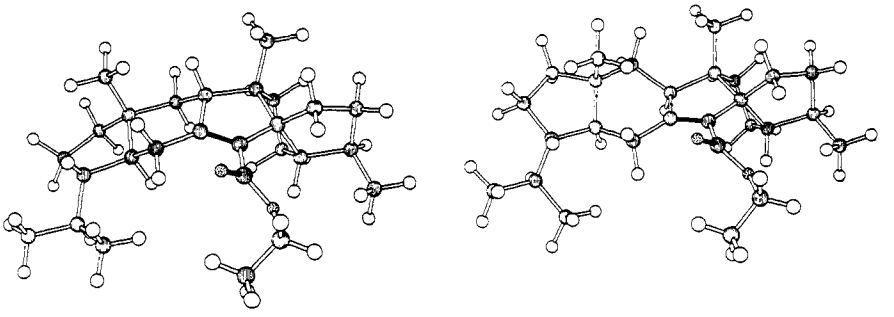


i ii

(83) Tietze, L. F.; Denzer, H.; Holdgrun, X.; Neumann, M. *Angew. Chem., Int. Ed. Eng.* **1987**, *26*, 1295.
(84) Enol ethers **57** were finally obtained in a reproducible way by distillation of **55** over $KHSO_4$. Some starting material remained but was easily removed by flash chromatography. The overall yield of **59** through this route was slightly higher than through enamine **58** and was preferred because of the much higher purity of the product.
(85) Piantadosi, C.; Skulason, V. G. *J. Pharm. Sci.* **1964**, *53*, 902.
(86) This supposition has been made on the basis of the higher yields obtained with "wet" solvents. See ref 20 and 88.
(87) In our hands, by the use of refluxed *p*-dichlorobenzene, no product was obtained from triene **60b**. The formation of hydrindan **61** did not take place below 280 °C (sealed tube, 8 h).
(88) When **60b** was heated in a sealed tube at 280 °C for 12 h in nonpurified *p*-dichlorobenzene, ketone **54** was obtained directly.
(89) Reaction at 350 °C in an autoclave gave a 4:1 nonseparable mixture of trans- and cis-fused hydrindans **61**.
(90) Application of 10000 psi at room temperature gave only recovered starting material. We thank Prof. Weinreb and his co-workers (Penn State University) for performing this experiment.
(91) TLC of the reaction mixture showed three spots: one was identified as the conjugated enol ester **61** (yellow upon development with anisaldehyde solution); the second one corresponded to an inseparable mixture of compounds suspected to contain the nonconjugated isomer **61** (this mixture was later hydrolyzed with HCl, and ketone **54** was isolated, confirming the presence of nonconjugated **61**); the third spot was unreacted starting material which was isolated and recycled (85% purity).



temperature (°C)	40a (%)	40b (%)
500	0.6	1
585-exo	1.7	1
585-endo	1	1
625	1	1
655	1.2	1



natural isomer **epimer**

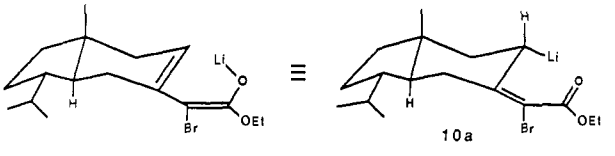
Δε (Kcal)
3.1†
2.4††

†: data from PC model; ††: data obtained by Prof. Paquette[65a]

Figure 9. MM2 conformations for **40a** and **40b** and the temperature profile for the rearrangement.

The bromo ester **10** was prepared as an *E*/*Z* mixture[92] by either of two procedures: Peterson olefination, bromination, and dehydrobromination,[93] or a one-step condensation of ethyl (trimethylsilyl)bromoacetate with **54**.[93,94]

The crucial union of **10** and **23** took place smoothly to afford vinylcyclopropanes **31** as a 1:1.5 mixture of exo/endo isomers. (See Table I.) From the foregoing discussion of the mechanism of the vinylcycloproanation, it should be evident that the ratios of exo/endo isomers did not reflect the *E*/*Z* composition of **10**. No evidence of proton abstraction from C-5 in **10** was found, and we believe that the reacting species in the addition of **10** to **23** was the *E* dienolate of **10a**.[9a] Of the four possible orientations



of this dienolate with enone **23**, the ones corresponding to **15a** and **15d** (see Figure 4) are more likely because of the bulk of the hydrindane nucleus. The disposition of either of these two arrangements is statistical and explains the almost 1:1 mixture of cyclopropanes. The vinylcyclopropanes were separated and thermolyzed separately or rearranged as a mixture to afford pentacycles **40a** and **40b** whose structure and stereochemistry were established by ^1H and ^{13}C NMR.[95] The temperature–product profile of these reactions is shown in Figure 9. It appears that lower temperatures favored the formation of the thermodynamically less stable epimer **40b**.

Molecular mechanics calculations, Figure 9, indicated an energy difference in the range of 2.4–3.1 kcal in favor of **40a**. These results were a bit puzzling, especially in the context of attempted isomerizations of retigeranic acid esters but were confirmed independently by Paquette in his full paper.[65a,b]

Pentacyclic ketone **40a**, possessing the natural configuration of retigeranic acid, was deoxygenated by means of Barton's procedure[69,96] to give ester **62a** via xanthate **63a** (Figure 10). The ^1H NMR spectrum of this material corresponded closely to the spectrum of the (methyl) ester provided to us by Prof. Paquette. Finally ester **62a** was hydrolyzed to **11** which had the rotation and ^1H NMR spectrum identical with natural retigeranic acid A, Figure 10. The same procedure transformed the epimer **40b** to **62b**, and attempts at base-catalyzed equilibration were made.[97] No equilibration was detected, although initial experiments with CD_3OD/CD_3ONa indicated complete exchange of the C-5b and C-10 protons in **62b**, as evidenced by the disappearance of the corresponding[98] NMR signals. The stereochemistry at C-5b in

(92) ^1H NMR confirmed a 3:1 mixture, but an exact assignment was not performed for these compounds.

(93) Taguchi, H.; Shimoji, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2529. Rathke, M. W.; Sullivan, D. F. *Syn. Commun.* **1973**, *3*, 67.

(94) Zapata, A.; Ferrer, G. F. *Syn. Commun.* **1986**, *16*, 1611. Emde, H.; Sinchen, G. *Liebigs Ann. Chem.* **1983**, 816.

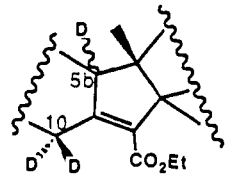
(95) A horizontal Vycor tube conditioned with $PbCO_3$ was used in a thermolysis oven at diffusion pump vacuum (10^{-4}–10^{-5} mmHg).

(96) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(97) MeONa in refluxing MeOH or *t*-BuOK in refluxing *t*-BuOH. No reaction was observed after 5 h.

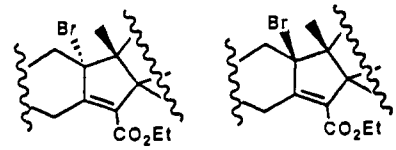
(98) The experiment was done in a sealed NMR tube. After 5 h at 40 °C, no change in NMR signals was observed. However, after 24 h, the peak corresponding to the proton at C-11 disappeared.

the trideuterated derivative **64** is unknown. The ultimate solution



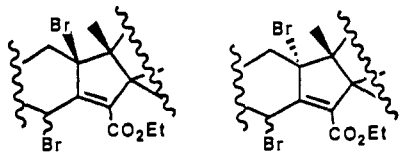
64

to the epimerization came as a result of considerations of the relative stabilities of **62a** and **62b**. Paquette's analysis of MM2 calculations revealed a misalignment of the C-5b proton of about 40°, thereby substantially decreasing the kinetic acidity of this hydrogen.[65b] When the base-catalyzed isomerization of **62b** failed and when the temperature of pyrolysis failed to elicit better control than about a 2:1 mixture of **40a** and **40b**, we turned to radical generation at C-5b as a means of equilibration, even though reports of related species present during dissolving metal reduction indicated preference for the β-side of the molecule at C-5b (performed on the ketone, not the ester!).[65a,b] Treatment of **62b** with an excess of NBS generated four compounds which can be speculatively assigned as **65a–d**. The scarcity of material precluded their full characterization.[99] This mixture was treated with *n*-Bu_3SnH and gave material that contained the correct ^1H NMR spectral pattern of the C-5b hydrogen in the natural, α-configuration, save for a slight change in the chemical shift.[100] Co-injection of this material with **62a** produced an enhanced signal in the capillary GC, so we assume that the allylic radical generated upon reduction abstracted a hydrogen from the α-face of the molecule. In this fashion, the synthesis of retigeranic acid (**11**) was accomplished in full stereo- and enantiocontrolled fashion.



65a

65b



65c

65d

In conclusion, it is clear that a potential second-generation synthesis of retigeranic acid should address the stereochemistry at C-5b. This point was not appreciably considered by any of the investigators, because it was assumed that a difference of 2.4 kcal, corresponding to a *K* value of 104 (!), should lead to complete equilibration. Unfortunately, the kinetic acidity of the C-5b proton, because of its misalignment, is such that base-catalyzed dienolate formation cannot take place. It seems that generation of a radical-leaving group at C-5b is all that is necessary to accomplish this task.

Summary

The foregoing discussion highlighted some recent developments in the two-step [2 + 3] cyclopentene annulation of enones. The precise regio- and stereochemical parameters, as well as the conditions, necessary to distinguish between the [2 + 3] and the [3 + 4] connectivity of the crotonate and enone units have been defined and exploited. The total synthesis of the pentacyclic sesterterpene retigeranic acid highlighted the application of this methodology in natural product synthesis. Current and future endeavors are aimed at a greater understanding of the stereoselectivity of the vinylcyclopropanation process and the application of the 4-oxycrotonates to annulations, leading to highly oxygenated cyclopentenes of the iridoid type. Enantiocontrolled syntheses of (−)-specionin and sanadaol by the application of the [2 + 3] and [3 + 4] protocol, respectively, are now in progress.

Experimental Section[101]

(*E*)- and (*Z*)-Ethyl 2-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-butenoate (6). To a solution of ethyl 4-hydroxy-2-butenoate (32.43 g, 0.25 mol) in DMF (150 mL) were added *tert*-butyldimethylsilyl chloride (45.2 g, 0.30 mol) and imidazole (25.5 g, 0.37 mol). Stirring was continued at room temperature for 4.5 h, whereupon TLC indicated that none of the alcohol remained. The reaction was quenched slowly with saturated aqueous $NaHCO_3$, and the crude reaction mixture was extracted with ether (3 × 100 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$, water, and brine and then dried over $MgSO_4$. Evaporation of the solvent gave 50.5 g (83%) of a very pale-yellow liquid. R_f = 0.62 (hexane/ethyl acetate, 3:1); ^1H NMR ($CDCl_3$) δ 1.04 (s, 3 H), 1.06 (s, 3 H), 1.90 (s, 9 H), 1.27 (t, 3 H, J = 7.1 Hz), 4.17 (q, 2 H, J = 7.1 Hz), 4.31 (dd, 2 H, J_1 = 3.4, J_2 = 2.4 Hz), 6.07 (dt, 1 H, J_1 = 15.5, J_2 = 2.4 Hz), 6.97 (dt, 1 H, J_1 = 15.5, J_2 = 3.4 Hz).

The crude ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-2-butenoate was dissolved in CCl_4 (150 mL) and cooled to 0 °C, and a solution of bromine (44.4 mL, 0.75 mol) in CCl_4 (100 mL) was added over 1.0 h. After the addition was complete, stirring was continued at 0 °C for 1.0 h and then at room temperature for 1.0 h. The crude reaction mixture was quenched with saturated aqueous Na_2SO_3 and diluted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent gave 66.72 g (79%) of a yellow oil pure enough to be used without distillation. ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H), 0.91 (s, 9 H), 1.31 (t, 3 H, J = 7.1 Hz), 4.0 (dd, 1 H, J = 11.8, J_2 = 1.9 Hz), 4.20–4.30 (m, 3 H), 4.40 (ddd, 1 H, J = 10.9, J_2 = 2.9, J_3 = 2.0 Hz), 4.58 (d, 1 H, J = 10.9 Hz).

The crude dibromides (66.72 g, 0.17 mol) in 250 mL of DME were cooled to 0 °C, and a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (27.4 mL, 0.18 mmol) in 100 mL of DME was added over 45 min. Stirring was continued at 0 °C for 1 h. The resulting black solution was then filtered through a plug of silica gel with ether as the eluent. The ether solution was washed twice with 3 N HCl. The aqueous layer was extracted twice with ether, and the combined ether extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave 40.5 g of a brown–orange liquid. The crude material was distilled in three portions to give 21.72 g (38%) of a 1:1 mixture of (*E*)- and (*Z*)-ethyl 2-bromocrotonates (**6**) as a pale-yellow liquid. There is significant loss of material due to decomposition of the bromides in the distillation pot. bp 90–105 °C/0.2 mmHg; IR (neat) 2915, 2815, 1717, 1615, 1250, 1225, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.07 (s, 6 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 1.31 (t, 6 H, J = 7.1 Hz), 4.19–4.30 (m, 4 H), 4.38 (d, 2 H, J = 4.9 Hz), 4.56 (d, 2 H, J = 4.9 Hz), 6.81 (t, 1 H, J = 4.9 Hz), 7.36 (t, 1 H, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$) δ −5.4 (CH_3, quadruple intensity), 14.0 (CH_3, double intensity), 18.2 (C, double intensity), 25.8 (CH_3, sextuplet intensity), 62.2 (CH_2), 62.5 (CH_2), 62.6 (CH_2), 63.7 (CH_2), 109.5 (C), 113.7 (C), 146.1 (CH), 150.9 (CH), 161.8 (C), 162.5 (C).

General Procedure for Cyclopropanation. To a stirred solution of lithium diisopropylamide (1.04 equiv, 5.2 mmol), prepared from diisopropylamine and *n*-butyllithium, in 8 mL of THF and HMPA (1.14 equiv, 5.7 mmol) at −110 °C was added a solution of the 2-bromo-2-butenoate[12] (1.0 equiv, 5.0 mmol) in 17 mL of THF, cooled to −105 °C, over a period of 25 min, while maintaining the temperature of the reaction at or below −100 °C. After the addition was complete, the re-

(99) The signal corresponding to the C-11 proton was absent in the ^1H NMR spectrum of the mixture of bromides **65**. The signals of the allylic methylene were also absent, and new signals appeared downfield, leading to the assignments of **65c** and **65d**.

(100) This signal was shifted relative to that of **62a**. We attribute this to the effect of the presence of nonpolar impurities derived from $(Bu_3Sn)_2$ or to the dilution of the sample (0.6 mg/mL).

(101) THF, ether, DME, and benzene were distilled from benzophenone ketyl, dichloromethane, and toluene from calcium hydride. Analytical TLC was performed on silica gel 60F–254 plates. Flash chromatography was performed on Kieselgel 60 (EM reagents, 230–400 mesh). Mass spectra were recorded on a Du Pont 20-491 or a Varian MAT-112 instrument (low resolution) or on a double-focusing Du Pont 21-110C or VGT instrument (exact mass). Infrared spectra were recorded on neat samples (NaCl plates) on a Perkin-Elmer 283B or 710B spectrometer. ^2H NMR spectra were obtained on a Bruker WP-270 instrument. Proton chemical shifts are reported in parts per million (ppm) with $CHCl_3$ as the reference (7.24 ppm). Carbon NMR spectra were recorded on a Bruker WP-270 or NR-80 instrument. Carbon chemical shifts are reported in ppm relative to the center line of the $CHCl_3$ triplet (77.0 ppm), and the multiplicity is indicated by CH_3, CH_2, CH, C (INEPT experiments).

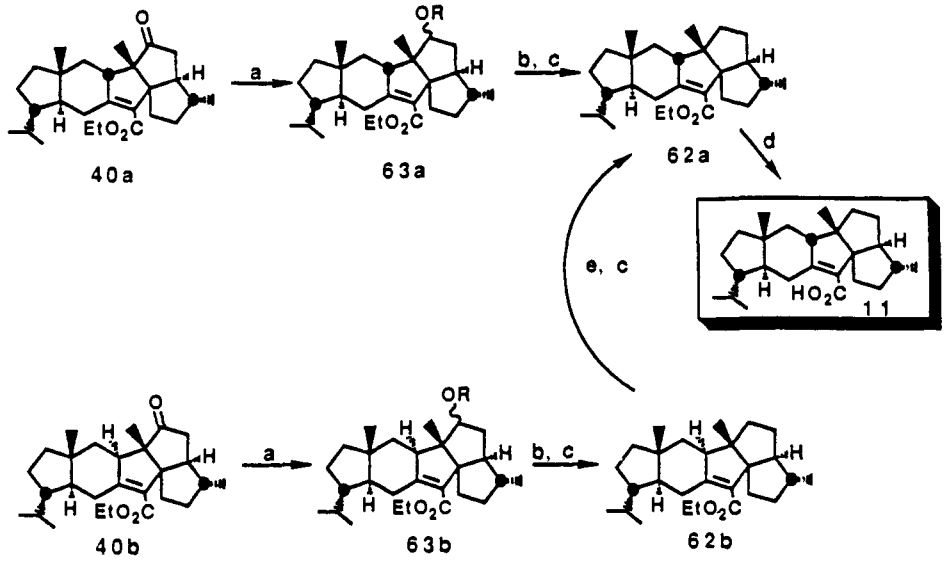


Figure 10. Synthesis of retigeranic acid.

action mixture was stirred for 15 min and then treated with a solution of the enone (1.0 equiv, 5.0 mmol) in 7 mL of THF cooled to −105 °C. This addition took 5 min and was also done at a rate that kept the temperature of the reaction at or below −100 °C. Stirring was continued between −100 and −110 °C over 0.5 h and at −78 °C for 1 h. The reaction mixture was then warmed to −50 °C over 0.5 h, quenched with saturated NH_4Cl solution, and diluted with ether. The ether layer was washed with 3 N HCl (1 × 15 mL), water (4 × 15 mL), and brine and then dried over Na_2SO_4. The solvent was removed in vacuo to give a mixture of *endo*- and *exo*-vinylcyclopropanes.

6-Carbethoxy-6-vinylbicyclo[3.1.0]hexan-2-one (8-exo and 8-endo Isomers). The general procedure for cyclopropanation was followed using ethyl 2-bromo-2-butenoate (5.0 mmol) and 2-cyclopentenone (5.0 mmol). Flash chromatography on 35 g of silica gel (5% deactivated with H_2O) with pentane/ether (15:1, 9:1, 3:1, 2:1) as eluant gave 260 mg of *endo*- and 390 mg of *exo*-vinylcyclopropanes (67% isolated yield). **8-exo**: R_f = 0.23 (hexane/ethyl acetate, 3:1); IR (neat) 2980, 1720, 1630, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7.0 Hz), 1.99–2.33 (m, 6 H), 4.10–4.22 (m, 2 H), 4.98 (d, 1 H, J = 17.3 Hz), 5.05 (d, 1 H, J = 10.7 Hz), 5.85 (dd, 1 H, J_1 = 17.3, J_2 = 10.7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 20.8 (CH_2), 36.3 (CH_2), 36.7 (CH), 41.0 (CH, C, double intensity), 61.6 (CH_2), 114.6 (CH_2), 135.3 (CH), 168.8 (C), 211.1 (C); MS (70 eV, rel intensity), *m/e* 194 (6, M^+), 138 (90), 110 (86), 91 (89), 77 (100), 65 (57), 53 (52). Calcd for $C_{11}H_{14}O_3$: 194.0943. Found: 194.0943. **8-endo**: R_f = 0.29 (hexane/ethyl acetate, 3:1); IR (neat) 2990, 1770, 1740, 1227 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7.0 Hz), 1.86–2.34 (m, 4 H), 2.56 (m, 2 H), 4.09 (q, 2 H, J = 7.0 Hz), 5.31 (d, 1 H, J = 17.3 Hz), 5.40 (d, 1 H, J = 10.6 Hz), 5.95 (dd, 1 H, J_1 = 17.3, J_2 = 10.6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3) 19.4 (CH_2), 35.4 (CH), 35.8 (C, CH_2), 40.8 (CH), 61.3 (CH_2), 122.6 (CH_2), 128.7 (CH), 170.4 (C), 212.3 (C); MS (CI, rel intensity), *m/e* 195 (M + 1, 100) 167 (8), 149 (12), 123 (11), 109 (15), 95 (29), 91 (20), 81 (62). Calcd for $C_{11}H_{15}O_3$: 195.1021. Found: 195.1015.

6-(Carbomethyloxy)-6-vinylbicyclo[3.1.0]hexan-2-one (18-exo and 18-endo Isomers). Following the general procedure for cyclopropanation using methyl 2-bromo-2-butenoate (10.0 mmol) and 2-cyclopentenone (10.0 mmol) and keeping the temperature at −78 °C, not −100 °C, gave after flash chromatography (silica gel, 19:1, 9:1 hexane/ethyl acetate) 697 mg of the exo isomer and 633 mg of the endo isomer (80% yield). **18-exo**: R_f = 0.55 (hexane/ether, 2:1); ^1H NMR ($CDCl_3$) δ 0.69 (m, 3 H, J = 7.5 Hz), 0.78–1.10 (m, 8 H), 1.30–1.55 (m, 2 H), 1.62 (m, 2 H), 1.78–2.05 (m, 3 H), 2.05–2.35 (m, 6 H), 4.65 (qd, 1 H, J_1 = 11.6, J_2 = 4.0 Hz), 4.99 (d, 1 H, J = 17.4 Hz), 5.03 (d, 1 H, J = 11.0 Hz), 5.85 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.7 (CH_3), 20.7 (CH), 20.9 (CH_2), 21.9 (CH_3), 23.0 (CH_2), 23.2 (CH_2), 25.7 (CH), 26.1 (CH), 31.5 (CH), 34.1 (CH_2), 36.4 (CH_2), 36.5 (CH_2), 36.8 (CH), 40.3 (CH_2), 40.9 (CH_2), 41.3 (CH), 46.7 (CH), 46.9 (CH), 76.0 (CH), 114.6 (CH_2), 114.8 (CH_2), 135.4 (CH), 135.5 (CH), 168.2 (C), 211.3 (C); MS (70 eV, rel intensity) *m/z* 166 (100), 148 (20), 138 (18), 124 (18), 110 (20), 97 (15), 91 (10), 83 (62), 77 (12), 69 (27), 55 (28). Calcd for $C_9H_{10}O_3$: 166.0630. Found: 166.0620. **18-endo**: R_f = 0.65 (hexane/ether, 2:1); ^1H NMR ($CDCl_3$) δ 0.65 (m, 3 H), 0.80 (m, 6 H), 0.85–1.00 (m, 3 H), 1.20–1.50 (m, 2 H), 1.55 (m, 2 H), 1.70 (m, 1 H), 1.78–2.30 (m, 5 H), 2.40–2.55 (m, 2 H), 4.50 (dt, 1 H, J_1 = 10.1, J_2 = 4.0 Hz), 5.88 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.5 (CH_3), 19.7 (CH_2), 20.6 (CH_3), 21.8 (CH_3), 23.2 (CH_2), 25.9 (CH), 31.2 (CH), 34.1 (CH_2), 35.3 (CH), 36.2 (CH_2), 40.6 (CH_2), 41.2 (CH), 47.1 (CH), 75.6 (CH), 122.9 (CH_2), 128.8 (CH), 170.0 (C), 212.9 (C); MS (70 eV, rel intensity), *m/z* 166 (100), 148 (25), 138 (20), 124 (35), 95 (18), 67 (83), 77 (13), 69 (25), 55 (28). Calcd for $C_9H_{10}O_3$: 166.0630. Found: 166.0615.

6-Carbethoxy-6-[((2-*tert*-butyldimethylsilyl)oxy)vinyl]bicyclo[3.1.0]-hexan-2-one (19-exo and 19-endo Isomers). Following the general procedure for cyclopropanation, using ethyl 2-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-butenoate (**6**) (3.4 mmol) ald 2-cyclopentenone (3.4 mmol) gave after flash chromatography (silica gel, 10% deactivated with H_2O; 9:1 hexane/ethyl acetate) 225 mg of the exo isomer and 159 mg of the endo isomer (38% yield). **19-exo**: R_f = 0.39 (hexane/ethyl acetate, 3:1); IR (neat) 2925, 1722, 1650, 1178, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H), 0.86 (s, 9 H), 1.22 (t, 3 H, J = 7.1 Hz), 2.01–2.28 (m, 6 H), 4.05–4.19 (m, 2 H), 5.10 (d, 1 H, J = 11.9 Hz), 6.40 (d, 1 H, J = 11.9 Hz); ^{13}C NMR ($CDCl_3$) δ −5.3 (CH_3, double intensity), 14.0 (CH_3), 18.2 (C), 20.7 (CH_2), 25.5 (CH_3, triple intensity), 35.7 (CH), 36.3 (CH_2), 37.7 (C), 40.7 (CH), 61.5 (CH_2), 108.9 (CH), 144.8 (CH), 169.5 (C), 212.0 (C); MS (CI, rel intensity), *m/e* 325 (32, M^+ + 1), 305 (19), 267 (19), 193 (100), 133 (57), 85 (16). Calcd for $C_{20}H_{32}O_6Si$: 324.1757. Found: 324.1788. **19-endo**: R_f = 0.49 (hexane/ethyl acetate, 3:1); IR (neat) 2912, 1720, 1650, 1252, 1218, 1162, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.106 (s, 3 H), 0.11 (s, 3 H), 0.88 (s, 9 H), 1.20 (t, 3 H, J = 7.2 Hz), 1.90–2.29 (m, 4 H), 2.48–2.56 (m, 2 H), 4.07 (q, 2 H, J = 7.2 Hz), 5.03 (d, 1 H, J = 12.3 Hz), 6.38 (d, 1 H, J = 12.3 Hz); ^{13}C NMR ($CDCl_3$) δ −5.3 (CH_3), −5.2 (CH_3), 14.2 (CH_3), 18.2 (C), 19.9 (CH_2), 25.6 (CH_3, triple intensity), 31.8 (CH_2), 35.1 (CH), 36.2 (C), 41.4 (CH), 61.6 (CH_2), 101.1 (CH), 148.0 (CH), 171.9 (C), 213.4 (C); MS (70 eV, rel intensity), *m/e* 324 (21, M^+), 267 (20), 223 (38), 193 (11), 105 (12), 103 (11), 75 (71), 73 (100), 59 (18). Calcd for $C_{20}H_{32}O_6Si$: 324.1757. Found: 324.1797.

7-Carbethoxy-7-vinylbicyclo[4.1.0]heptan-2-one (25-exo and 25-endo Isomers). Following the general procedure for vinylcyclopropanation, using ethyl 2-bromo-2-butenoate (5.0 mmol) and 2-cyclohexenone (5.0 mmol) gave after flash chromatography (silica gel, 10% deactivated with H_2O; 19:1, 9:1, 3:1, hexane/ether) 270 mg of the endo isomer, 480 mg of the exo isomer, and 120 mg of a mixture of both isomers (90% yield). **25-exo**: R_f = 0.25 (hexane/ethyl acetate, 3:1); IR (neat) 2950, 1725, 1700, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (t, 3 H, J = 7.2 Hz), 1.55–2.3 (m, 8 H), 4.12 (qd, 2 H, J_1 = 7.2, J_2 = 1.5 Hz), 5.0 (d, 1 H, J = 17.2 Hz), 5.0 (d, 1 H, J = 10.6 Hz), 5.88 (dd, 1 H, J_1 = 17.2, J_2 = 10.6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 18.9 (CH_2), 21.8 (CH_2), 30.8 (CH), 33.6 (CH), 38.0 (CH_2), 40.8 (C), 61.5 (CH_2), 114.0 (CH_2), 136.9 (CH), 169.1 (C), 205.1 (C); MS (70 eV, rel intensity), *m/e* 208 (30, M^+), 180 (31), 162 (100), 134 (72), 79 (78). Calcd for $C_{12}H_{16}O_3$: 208.1099. Found: 208.1111. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 68.54; H, 7.83. **25-endo**: R_f = 0.35 (hexane/ethyl acetate, 3:1); IR (neat) 2950, 1720, 1705, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (t, 3 H, J = 7.0 Hz), 1.60–1.87 (m, 3 H), 1.97–2.24 (m, 4 H), 2.45 (d,

1 H, J = 7.0 Hz), 4.07 (q, 2 H, J = 7.0 Hz), 5.21 (dd, 1 H, J_1 = 17.5, J_2 = 0.8 Hz), 5.42 (d, 1 H, J = 10.5 Hz), 5.94 (dd, 1 H, J_1 = 17.5, J_2 = 10.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 18.2 (CH_2), 22.9 (CH_2), 34.1 (CH), 36.6 (C), 39.2 (CH_2), 61.5 (CH_2), 123.7 (CH_2), 130.1 (CH), 171.9 (C), 206.7 (C); MS (70 eV, rel intensity), m/e 208 (13, M^+), 180 (31), 162 (100), 134 (62), 79 (73). Calcd for $C_{12}H_{16}O_3$: 208.1099. Found: 208.1101.

8-Carbethoxy-8-vinylbicyclo[5.1.0]octan-2-one (26-exo and 26-endo Isomers). Following the general procedure for vinylcyclopropanation using ethyl 2-bromo-2-butenoate (5.0 mmol) and 2-cycloheptenone (**21**) (5.0 mmol) gave after flash chromatography (silica gel; 19:1, 9:1, 3:1 hexane/ether) 980 mg of a 1.4:1 mixture of *exo*- and *endo*-vinylcyclopropanes, respectively (83% yield). For analytical purposes, the isomers were separated by preparative TLC (95:5 hexane/ethyl acetate). **26-exo**: R_f = 0.45 (hexane/ethyl acetate, 7:3); IR (neat) 3050, 2965, 1730, 1710, 1650, 1300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.2 Hz), 1.55–1.73 (m, 3 H), 1.73–1.9 (m, 3 H), 2.02–2.12 (m, 1 H), 2.18 (d, 1 H, J = 8.5 Hz), 2.45–2.55 (m, 2 H), 4.15 (qd, 2 H, J_1 = 7.2, J_2 = 1.3 Hz), 4.98 (d, 1 H, J = 17.2 Hz), 5.00 (d, 1 H, J = 10.2 Hz), 6.34 (dd, 1 H, J_1 = 17.2, J_2 = 10.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 21.6 (CH_2, double intensity), 25.4 (CH_2), 30.1 (CH), 36.6 (C), 38.8 (CH), 42.7 (CH_2), 60.9 (CH_2), 112.8 (CH_2), 136.8 (CH), 169.5 (C), 206.3 (C); MS (70 eV, rel intensity), m/e 222 (15, M^+), 194 (50), 177 (90), 148 (90), 120 (60), 105 (50), 91 (95), 79 (100). Calcd for $C_{13}H_{18}O_3$: 222.1256. Found: 222.0899. **26-endo**: R_f = 0.58 (hexane/ethyl acetate, 7:3), IR (neat) 2960, 1735, 1710, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7.1 Hz), 1.35–1.65 (m, 3 H), 1.78–2.0 (m, 3 H), 2.09–2.21 (m, 1 H), 2.29–2.40 (m, 1 H), 2.48–2.61 (m, 2 H), 4.11 (q, 2 H, J = 7.1 Hz), 5.26 (dd, 1 H, J_1 = 17.7, J_2 = 1.6 Hz), 5.38 (dd, 1 H, J_1 = 10.9, J_2 = 1.6 Hz), 6.01 (dd, 1 H, J_1 = 17.7, J_2 = 10.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.9 (CH_2), 23.8 (CH_2, double intensity), 25.7 (CH), 32.0 (C), 39.1 (CH), 43.8 (CH_2), 61.4 (CH_2), 121.9 (CH_2), 129.6 (CH), 172.5 (C), 205.0 (C); MS (70 eV, rel intensity), m/e 222 (M^+, 5), 176 (100), 148 (50), 120 (20), 105 (30), 91 (53), 79 (90). Calcd for $C_{13}H_{18}O_3$: 222.1256. Found: 222.1254.

(3*S*,4*R*)-6-Carbethoxy-3,4-(isopropylidenedioxy)-6-vinylbicyclo[3.1.0]hexan-2-one (27-exo and 27-endo Isomers). Following the general procedure for vinylcyclopropanation using ethyl 2-bromo-2-butenoate (0.64 mmol) and (2*S*,3*R*)-2,3-(isopropylidenedioxy)cyclopent-4-enone (**22**) (0.64 mmol) gave after flash chromatography (silica gel, 10% deactivated with H_2O; 6:1 hexane/ethyl acetate) 111 mg of a mixture of *endo*- and *exo*-vinylcyclopropanes (72% yield). For analytical purposes, the isomers were separated by preparative TLC (6:1 hexane/ethyl acetate, two elutions). **27-exo**: R_f = 0.48 (hexane/ethyl acetate, 2:1); $[\alpha]_D$ +14.2° (*c* 0.38, MeOH); IR (neat) 2970, 1737, 1722, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7.0 Hz), 1.29 (s, 3 H), 1.42 (s, 3 H), 2.40 (d, 1 H, J = 5.5 Hz), 2.54 (d, 1 H, J = 5.5 Hz), 4.13 (q, 2 H, J = 7.0 Hz), 4.40 (d, 1 H, J = 5.0 Hz), 4.65 (d, 1 H, J = 5.0 Hz), 4.96 (d, 1 H, J = 17.2 Hz), 5.06 (d, 1 H, J = 10.7 Hz), 6.15 (dd, 1 H, J_1 = 17.2, J_2 = 10.7 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 24.7 (CH_3), 26.8 (CH_3), 39.7 (CH), 41.0 (C), 41.2 (CH), 62.3 (CH_2), 76.6 (CH), 81.8 (CH), 112.5 (C), 115.2 (CH_2), 133.9 (CH), 169.4 (C), 204.5 (C); MS (70 eV rel intensity), m/e 266 (11, M^+), 162 (46), 138 (85), 123 (79), 107 (100), 79 (95), 77 (92). Calcd for $C_{14}H_{14}O_5$: 266.1154. Found: 266.1146. **27-endo**: R_f = 0.42 (hexane/ethyl acetate, 2:1); IR (neat) 2990, 1745, 1728, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7.1 Hz), 1.29 (s, 3 H), 1.40 (s, 3 H), 2.69 (d, 1 H, J = 5.6 Hz), 2.86 (d, 1 H, J = 5.6 Hz), 4.08 (d, 1 H, J = 5.1 Hz), 4.12 (q, 2 H, J = 7.1 Hz), 4.65 (d, 1 H, J = 5.1 Hz), 5.24 (d, 1 H, J = 17.5 Hz), 5.44 (d, 1 H, J = 10.4 Hz), 5.99 (dd, 1 H, J_1 = 17.5, J_2 = 10.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3) 25.0 (CH_3), 27.0 (CH_3), 36.9 (C), 38.6 (CH), 38.8 (CH), 62.1 (CH_2), 75.9 (CH), 80.1 (CH), 112.7 (C), 124.4 (CH_2), 129.4 (CH), 169.5 (C), 207.1 (C); MS (70 eV, rel intensity), m/e 266 (7, M^+), 251 (42), 207 (34), 135 (42), 123 (45), 107 (100), 79 (56), 77 (54). Calcd for $C_{14}H_{18}O_5$: 266.1154. Found: 266.1159.

(3*S*,4*R*)-6-[(2-*tert*-Butyldimethylsilyl)oxy]-6-carbethoxy-3,4-(isopropylidenedioxy)bicyclo[3.1.0]hexan-2-one (28-exo and 28-endo Isomers). Following the general procedure for vinylcyclopropanation, using ethyl 2-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-butenoate (1.7 mmol) and (2*S*,3*R*)-2,3-(isopropylidenedioxy)cyclopent-4-enone (**22**) (1.7 mmol) gave after flash chromatography (silica gel, 10% deactivated with H_2O; 10:1 hexane/ethyl acetate) 67.4 mg of *endo*- and 178.2 mg of *exo*-vinylcyclopropanes (36% yield). **28-exo**: R_f = 0.12 (hexane/ethyl acetate, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6 H), 0.89 (s, 9 H), 1.23 (t, 3 H, J = 7.1 Hz), 1.32 (s, 3 H), 1.46 (s, 3 H), 2.36 (d, 1 H, J = 5.5 Hz), 2.51 (d, 1 H, J = 5.5 Hz), 4.12 (q, 2 H, J = 7.1 Hz), 4.43 (d, 1 H, J = 5.0 Hz), 4.68 (d, 1 H, J = 5.0 Hz), 5.22 (d, 1 H, J = 12.0 Hz), 6.39 (d, 1 H, J = 12.0 Hz). **28-endo**: R_f = 0.18 (hexane/ethyl acetate, 9:1); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.85 (s, 9 H), 1.21 (t, 3 H, J = 7.1 Hz), 1.31 (s, 3 H), 1.41 (s, 3 H), 2.67 (d, 1 H, J = 5.6 Hz), 2.82 (d, 1 H, J = 5.6 Hz), 4.05–4.14 (m, 3 H), 4.64 (d, 1 H, J = 5.1 Hz), 5.02 (d, 1 H, J = 12.2 Hz), 6.33 (d, 1 H, J = 12.2 Hz).

General Procedure for Pyrolysis. A sample of the vinylcyclopropane was evaporated (10^{-4} mmHg) through a horizontally situated Vycor tube (41 cm, 5-mm i.d.) which was heated to the specified temperature after being thoroughly cleaned (nitric acid; 50% KOH) and preheated with a slurry of $PbCO_3$. The pyrolysate was condensed in a trap cooled with liquid nitrogen. The apparatus was rinsed with ether, the solution was filtered to remove inorganic impurities, and the solvent was evaporated to give the crude pyrolysate.

2-Carbethoxybicyclo[3.3.0]oct-2-en-6-one (1). The vinylcyclopropane **8-endo** (79 mg, 0.41 mmol) was pyrolyzed (550 °C) according to the general procedure to give after preparative TLC (9:1 hexane/ethyl acetate, three elutions) 23 mg of diquinane **1** (43% yield). R_f = 0.35 (hexane/ethyl acetate, 3:1); IR (neat) 2950, 1732, 1709, 1620, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz), 2.0–2.35 (m, 4 H), 2.65–2.72 (m, 2 H), 2.76–2.84 (m, 1 H), 3.69–3.78 (m, 1 H), 4.12–4.25 (m, 2 H), 6.78 (dd, 1 H, J_1 = 4.5, J_2 = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 25.0 (CH_2), 36.3 (CH_2), 36.6 (CH_2), 46.8 (CH), 49.4 (CH), 60.3 (CH_2), 138.0 (C), 143.2 (CH), 164.4 (C), 222.1 (C); MS (70, rel intensity), m/e 194 (M^+, 100), 166 (20), 149 (45), 138 (22), 121 (30), 105 (33), 93 (35), 79 (56), 65 (60). Calcd for $C_{11}H_{14}O_3$: 194.0943. Found: 194.0932.

7-Carbethoxybicyclo[4.3.0]non-7-en-2-one (32). Vinylcyclopropane **25-exo** (770 mg, 3.7 mmol) was pyrolyzed (600 °C) according to the general procedure to give after preparative TLC (9:1 hexane/ethyl acetate, three elutions) 146 mg of hydrindane **32** (19% yield). R_f = 0.19 (hexane/ethyl acetate, 3:1); IR (neat) 2950, 1720, 1710, 1260, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7.2 Hz), 1.32–1.50 (m, 1 H), 1.7–1.9 (m, 2 H), 2.1–2.2 (m, 1 H), 2.3–2.4 (m, 2 H), 2.55–2.83 (m, 2 H), 2.98 (dd, 1 H, J_1 = 17.0, J_2 = 8.8 Hz), 3.27–3.40 (m, 1 H), 4.18 (m, 2 H), 6.73 (dd, 1 H, J_1 = 4.5, J_2 = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 22.1 (CH_2), 27.3 (CH_2), 34.4 (CH_2), 39.1 (CH_2), 46.1 (CH), 50.4 (CH), 60.2 (CH_2), 139.6 (C), 141.9 (CH), 164.4 (C), 213.2 (C); MS (70 eV, rel intensity), m/e 208 (65, M^+), 179 (20), 162 (40), 135 (100), 117 (50), 91 (45), 79 (60), 65 (40). Calcd for $C_{12}H_{16}O_3$: 208.1099. Found: 208.1105.

8-Carbethoxybicyclo[5.3.0]dec-8-en-2-one (33). A mixture of *endo*- and *exo*-vinylcyclopropanes **26** (237 mg, 1.07 mmol) was pyrolyzed (600 °C) according to the general procedure to give after flash chromatography (silica gel; 98:2, 95:5, 9:1 hexane/ether) and then preparative TLC 50 mg of hydroazulene **33** (21% yield). R_f = 0.28 (hexane/ether, 7:3); IR (neat) 2920, 2240, 1700, 1628, 1255, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (m, 1 H), 1.26 (t, 3 H, J = 7.2 Hz), 1.42–1.67 (m, 2 H), 1.80–2.02 (m, 3 H), 2.35–2.48 (m, 2 H), 2.55–2.66 (m, 1 H), 2.98 (m, 1 H), 3.26 (br t, 1 H, J = 8.9 Hz), 3.48 (q, 1 H, J = 8.9 Hz), 4.16 (q, 2 H, J = 7.2 Hz), 6.68 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 26.1 (CH_2), 29.0 (CH_2), 30.1 (CH_2), 31.7 (CH_2), 43.1 (CH_2), 45.5 (CH), 55.7 (CH), 60.1 (CH_2), 137.5 (C), 141.6 (CH), 164.3 (C), 211.8 (C); MS (70, rel intensity), m/e 222 (43, M^+), 176 (76), 149 (60), 91 (90), 79 (90), 65 (77), 55 (100). Calcd for $C_{13}H_{18}O_3$: 222.1256. Found: 222.1275.

4-[(*tert*-Butyldimethylsilyl)oxy]-2-carbethoxybicyclo[3.3.0]oct-2-en-6-one (35-exo and 35-endo Isomers). The vinylcyclopropanes **19-exo** and **19-endo** (53.5 mg, 0.17 mmol) were pyrolyzed (550 °C) according to the general procedure to give after preparative TLC (hexane/ethyl acetate, 8:1, two elutions) 8.0 mg of the exo isomer and 20 mg of the endo isomer (52% yield). **35-exo**: R_f = 0.22 (hexane/ethyl acetate, 9:1); IR (neat) 2950, 1735, 1720, 1629, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.87 (s, 9 H), 1.30 (t, 3 H, J = 7.1 Hz), 2.03–2.30 (m, 4 H), 2.74 (d, 1 H, J = 7.4 Hz), 3.89 (m, 1 H), 4.15–1.28 (m, 2 H), 4.83 (br s, 1 H), 6.55 (t, 1 H, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ –4.7 (CH_3, double intensity), 14.2 (CH_3), 18.1 (C), 24.2 (CH_2), 25.8 (CH_3, triple intensity), 36.6 (CH_2), 45.6 (CH), 60.6 (CH, CH_2), 79.4 (CH), 140.8 (C), 142.6 (CH), 164.4 (C), 218.3 (C); MS (CI, rel intensity), m/e 325 (20, M^+ + 1), 267 (21), 193 (100), 133 (42). Calcd for $C_{17}H_{29}O_4Si$: 325.1835. Found: 325.1872. **35-endo**: R_f = 0.18 (hexane/ethyl acetate, 9:1); IR (neat) 2930, 1740, 1710, 1632, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.84 (s, 9 H), 1.30 (t, 3 H, J = 7.1 Hz), 1.94–2.37 (m, 4 H), 2.91 (t, 1 H, J = 8.8 Hz), 3.50–3.61 (m, 1 H), 4.13–4.33 (m, 2 H), 5.03 (dd, 1 H, J_1 = 8.8, J_2 = 2.0 Hz), 6.53 (t, 1 H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ –5.1 (CH_3, double intensity), 14.1 (CH_3), 18.1 (C), 25.4 (CH_2), 25.7 (CH_3, triple intensity), 38.6 (CH_2), 45.7 (CH), 53.6 (CH), 60.5 (CH_2), 77.0 (CH), 139.8 (C), 141.8 (CH), 164.4 (C), 214.3 (C); MS (CI, rel intensity), m/e 325 (42, M^+ + 1), 267 (30), 193 (100), 133 (21). Calcd for $C_{17}H_{29}O_4Si$: 325.1835. Found: 325.1866.

(7*S*,8*R*)-2-Carbethoxy-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-en-6-one (37). Vinylcyclopropane **27-exo** (41 mg, 0.15 mmol) was pyrolyzed (550 °C) according to the general procedure to give after preparative TLC (9:1 hexane/ethyl acetate, two elutions; 6:1, one elution) 21

mg of diquinane **37** (51% yield). $[\alpha]_D$ + 64.4° (*c* 0.25, MeOH); R_f = 0.35 (hexane/ethyl acetate, 3:1); IR (neat) 2980, 2930, 1755, 1712, 1621, 1370, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7.1 Hz), 1.30 (s, 3 H), 1.38 (s, 3 H), 2.67–2.75 (m, 2 H), 3.18 (m, 1 H), 3.79 (m, 1 H), 4.12 (d, 1 H, J = 5.1 Hz), 4.19 (qd, 2 H, J_1 = 7.1, J_2 = 1.8 Hz), 4.99 (d, 1 H, J = 5.1 Hz), 6.74 (dd, 1 H, J_1 = 4.8, J_2 = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 25.0 (CH_3), 27.0 (CH_3), 36.1 (CH_2), 46.7 (CH), 50.3 (CH), 60.6 (CH_2), 78.9 (CH, double intensity), 112.2 (C), 135.1 (C), 145.4 (CH), 163.7 (C), 217.3 (C); MS (70 eV, rel intensity), *m/e* 266 (8, M^+), 251 (29), 208 (46), 134 (48), 100 (100), 85 (87), 79 (75). Calcd for $C_{14}H_{18}O_5$: 266.1154. Found: 266.1171.

(7*S*,8*R*)-4-*endo*-[(*tert*-Butyldimethylsilyl)oxy]-2-carbethoxy-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-en-6-one (38). Vinylcyclopropane **28-exo** (158 mg, 0.40 mmol) was pyrolyzed (525 °C) according to the general procedure to give after flash chromatography (silica gel, 10% deactivated with H_2O; 19:1, 15:1, 12:1 hexane/ethyl acetate) 118 mg of diquinane **38** (75% yield). R_f = 0.35 (hexane/ethyl acetate, 8:1); IR (neat) 2910, 2240, 1755, 1716, 1636, 1247, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.79 (s, 9 H), 1.30 (t, 3 H, J = 7.1 Hz), 3.25 (t, 1 H, J = 9.0 Hz), 3.58 (br d, 1 H, J = 9.0 Hz), 4.18–4.32 (m, 2 H), 4.35 (d, 1 H, J = 5.1 Hz), 4.58 (d, 1 H, J = 5.1 Hz), 5.02 (dd, 1 H, J_1 = 9.0, J_2 = 2.2 Hz), 6.56 (t, 1 H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ −5.8 (CH_3), −5.7 (CH_3), 13.6 (CH_3), 17.5 (C), 25.1 (CH_3, triple intensity), 26.4 (CH_3), 26.5 (CH_3), 47.6 (CH), 51.9 (CH), 60.3 (CH_2), 76.2 (CH), 77.5 (CH), 80.6 (CH), 111.7 (C), 136.4 (C), 142.9 (CH), 163.2 (C), 210.7 (C); MS (70, rel intensity), *m/e* 396 (1.5, M^+), 339 (26), 281 (100), 179 (13), 165 (19), 85 (13), 75 (55), 73 (59), 57 (18). Calcd for $C_{20}H_{32}O_6Si$: 396.1968. Found: 369.1934.

(*R*)-7,7-Dimethoxy-5-isopropylheptan-2-one (55). A solution of menthene (**52**) (27 g, 0.20 mol) in CH_2Cl_2 (50 mL) was added to 100 mL of methanol, placed in a glass gas-washing bottle equipped with a glass frit terminated inlet tube, and cooled to −78 °C (dry ice/acetone). Ozone was bubbled through this solution until a lavender blue color persisted (saturated solution), which usually took 1.5 h. After the solution was purged with N_2 to displace residual ozone, *p*-toluenesulfonic acid (0.5 g) was added and the mixture transferred to a round-bottom flask. Methyl sulfide (120 g, 1.93 mol) was added slowly at 0 °C to avoid any boiling over, and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated, diluted with 50 mL of ethyl ether, and poured into cold saturated $NaHCO_3$, and the aqueous layer was extracted with ether (3 × 50 mL). The organic layers were combined, washed with brine (3 × 50 mL), dried, and evaporated to give 37 g (87%) of essentially pure acetal, suitable for use in the next step. R_f = 0.18 (hexane/ether, 7:3); bp (Kugelrohr temperature) 80–100 °C (0.2 mmHg); $[\alpha]_D$ +3.2° (*c* 5.50, MeOH); IR (neat) 2950, 2830, 1720, 1190, 1160, 1125, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (d, 3 H, J = 7.0 Hz), 0.82 (d, 3 H, J = 7.0 Hz), 1.20–1.30 (m, 1 H), 1.30–1.38 (m, 1 H), 1.40–1.73 (m, 4 H), 2.10 (s, 3 H), 2.40 (t, 2 H, J = 7.0 Hz), 3.25 (s, 3 H), 3.29 (s, 3 H), 4.39 (t, 1 H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_3), 19.2 (CH_3), 24.8 (CH_2), 29.5 (CH), 29.8 (CH_3), 33.4 (CH_2), 39.1 (CH), 41.8 (CH_2), 52.3 (CH_3), 53.2 (CH_3), 103.9 (CH), 208.9 (C); (70 eV, rel intensity), *m/e* 215 (18, $(M - 1)^+$), 199 (23), 185 (9), 141 (22), 81 (78), 69 (100). Calcd for $C_{12}H_{23}O_3$: 215.1647. Found: 215.1653.

(*E*)- and (*Z*)-(*S*)-7-Methoxy-5-isopropyl-6-hepten-2-one (57). (*R*)-7,7-Dimethoxy-5-isopropylheptan-2-one (**55**) (17.6 g, 81.5 mmol) was distilled over potassium hydrogen sulfate (0.2 g) at 90–100 °C (1.5 mmHg). The distillate (11.5 g) was purified by column chromatography on silica gel to give 6.65 g (44%) of an inseparable mixture of enol ethers (*E*:*Z* = 1.2:1) and 3.0 g (17%) of starting ketoacetal. The mixture of enol ethers was used in the next step. R_f = 0.38 (hexane/ether, 7:3). ^1H NMR of the mixture ($CDCl_3$) δ 0.78–0.85 (four doublets, 12 H), 1.21–1.78 (m, 6 H), 2.10 (s, 6 H), 2.15–2.50 (m, 6 H), 3.48 (s, 3 H, *E* isomer), 3.50 (s, 3 H, *Z* isomer), 4.03 (dd, 1 H, J_1 = 10.5, J_2 = 5.8 Hz, *Z* isomer), 4.36 (dd, 1 H, J_1 = 12.8, J_2 = 10.5 Hz, *E* isomer), 5.95 (d, 1 H, J = 5.8 Hz, *Z* isomer), 6.15 (d, 1 H, J = 12.8 Hz, *E* isomer). ^{13}C NMR of *E* isomer ($CDCl_3$) δ 18.6 (CH_3), 20.5 (CH_3), 26.9 (CH_2), 29.7 (CH_3), 32.3 (CH), 41.8 (CH_2), 44.4 (CH), 55.6 (CH_3), 103.5 (CH), 147.6 (CH), 208.3 (C); ^{13}C NMR of *Z* isomer ($CDCl_3$) δ 18.4 (CH_3), 20.3 (CH_3), 26.5 (CH_2), 29.7 (CH_3), 31.9 (CH), 39.7 (CH), 41.8 (CH_2), 59.0 (CH_3), 108.3 (CH), 147.0 (CH), 208.3 (C).

(*S*)-5-Oxo-2-isopropylhexanal (59). (a) From Enol Ethers 57. A mixture of (*E*)- and (*Z*)-(*S*)-7-methoxy-5-isopropyl-6-hepten-2-one (**57**) (16.2 g, 88.0 mmol) (*E*:*Z* = 1.2:1) was dissolved in 2:1 $MeOH/CH_2Cl_2$ (150 mL), the mixture was cooled to −78 °C, and O_3 was bubbled through it until the appearance of a blue color. Nitrogen was then bubbled through the solution at −78 °C until thee excess O_3 was eliminated. Dimethyl sulfide (65 mL, 885 mmol) was added at 0 °C, and the reaction mixture was stirred overnight at room temperature. The solvent was removed in vacuo, and the crude product was dissolved in ethyl ether (50 mL) and washed with brine (3 × 30 mL). The organic layer was then dried, concentrated in vacuo, and distilled using a Kugelrohr apparatus. Pure ketoaldehyde (11.0 g, 80%) was obtained. R_f = 0.17 (hexane/ether, 4:1); bp (Kugelrohr temperature) 125 °C (0.25 mmHg); $[\alpha]_D$ +40° (*c* 1.72, $CDCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (d, 3 H, J = 7.0 Hz), 0.98 (d, 3 H, J = 7.0 Hz), 1.70–1.90 (m, 2 H), 2.00–2.08 (m, 2 H), 2.10 (s, 3 H), 2.25–2.55 (m, 2 H), 9.60 (d, 1 H, J = 3.1 Hz); ^{13}C NMR ($CDCl_3$) δ 19.5 (CH_3), 19.5 (CH_2), 20.0 (CH_3), 28.4 (CH), 29.9 (CH_3), 41.3 (CH_2), 57.5 (CH), 205.1 (CH), 207.8 (C).

(b) From (*S*)-3-Isopropyl-6-oxo-1-piperidinohept-1-ene (58). (*S*)-3-Isopropyl-6-oxo-1-piperidinohept-1-ene[79] (**58**) (10.7 g, 45 mmol) was dissolved in CH_2Cl_2 (150 mL), the mixture was cooled to −78 °C, and ozone was bubbled through it until the appearance of a permanent blue color. Dimethyl sulfide (28 g, 450 mmol) was added dropwise at −20 °C, and the mixture as stirred at room temperature for 24 h. Solvent was evaporated in vacuo, and the residue was distilled in vacuo (70–90 °C, 0.25 mmHg) and chromatographed on silica gel (hexane/ether, 4:1) to yield 2.1 g (30%) of ketoaldehyde **59**.

(*E*)- and (*Z*)-(1*R*,6*S*,7*S*)-4-(Bromocarbethoxymethylidene)-1-methyl-7-isopropylbicyclo[4.3.0]nonane (10). Ethyl (trimethylsilyl)-acetate (1.93 g, 12.06 mmol) in THF (10 mL) was added dropwise to a solution of lithium dicyclohexylamide prepared from dicyclohexylamine (2.19 g, 12.06 mmol) and *n*-butyllithium (4.8 mL, 12.06 mmol; 2.5 M in hexane) in THF (10 mL) at −78 °C. After the mixture stirred for 30 min, a solution of (1*R*,6*S*,7*S*)-7-isopropyl-1-methylbicyclo[4.3.0]nonan-4-one (**54**) (1.17 g, 6.03 mmol) in THF (10 mL) was added dropwise. The reaction mixture was then slowly warmed to room temperature and, after 1 h, quenched with cold 3 N HCl (10 mL) and ethyl ether (20 mL). The organic layer was washed with 3 N HCl (5 mL) and the combined aqueous layer extracted with ethyl ether (3 × 8 mL). The organic layers were combined, washed with brine (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was filtered through a plug of silica gel to yield 1.19 g (75%) of α,β-unsaturated esters. These esters were dissolved in CCl_4 (20 mL), the solution was cooled to 0 °C, and a solution of bromine (1.08 g, 6.8 mmol) in CCl_4 (3 mL) was added dropwise at 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.76 g, 5 mmol) was added dropwise at 0 °C. The reaction was quenched with cold 3 N HCl (5 mL) and ethyl ether (10 mL). The aqueous layer was extracted with ethyl ether (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL), dried (Na_2SO_4), and evaporated in vacuo. The crude product was filtered through a plug of silica gel to yield 1.45 g (70 % from ketone **54**) of a 3:1 (more polar:less polar) mixture of *E* and *Z* bromides. **10-less polar**: R_f = 0.57 (hexane/ether = 95:5); bp (Kugelrohr temperature) 200 °C (0.025 mmHg); IR (neat) 2950, 2810, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (d, 3 H, J = 7.0 Hz), 0.85 (s, 3 H), 0.88 (d, 3 H, J = 7.0 Hz), 1.00–1.20 (m, 2 H), 1.30 (t, 3 H, J = 7.0 Hz), 1.20–1.80 (m, 7 H), 1.85 (t, 1 H, J = 13.9 Hz), 2.20 (dt, 1 H, J = 13.9, 5.8 Hz), 2.93 (m, 2 H), 4.25 (q, 2 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 17.3 (CH_3), 18.0 (CH_3), 21.7 (CH_3), 24.4 (CH_2), 29.5 (CH), 30.8 (CH_2), 31.9 (CH_2), 38.5 (CH_2), 41.3 (Ce, 46.1 (CH), 50.6 (CH), 61.7 (CH_2), 106.0 (C), 149.9 (C), 164.8 (C). **10-more polar**: R_f = 0.47 (hexane/ether, 95:5); bp (Kugelrohr temperature) 200 °C (0.025 mmHg); IR (neat) 2950, 2810, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (d, 3 H, J = 7.0 Hz), 0.84 (s, 3 H), 0.90 (d, 3 H, J = 7.0 Hz), 1.00–1.20 (m, 2 H), 1.20–1.35 (m, 1 H), 1.30 (t, 3 H, J = 6.0 Hz), 1.35–1.78 (m, 6 H), 1.82 (t, 1 H, J = 15.0 Hz), 2.25 (dt, 1 H, J = 15.0, 6.0 Hz), 2.90 (br d, 1 H, J = 15.0 Hz), 3.00 (br d, 1 H, J = 15.0 Hz), 4.25 (q, 2 H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 17.5 (CH_3), 18.3 (CH_3), 21.7 (CH_3), 24.4 (CH_2), 28.7 (CH_2), 29.7 (CH), 34.6 (CH_2), 38.4 (CH_2), 39.0 (CH_2), 41.4 (C), 46.4 (CH), 50.3 (CH), 61.7 (CH_2), 106.0 (C), 150.5 (C), 164.8 (C).

(1*S*)-(1α,3β,6α,7α)-2-Carbethoxy-3,7-dimethyl-2-[4-[(1β,6α,7α)-1-methyl-7-isopropylbicyclo[4.3.0]non-3-enyl]]-4-oxobicyclo[4.3.0^{1,3}]nonane (31-exo and 31-endo Isomers). Lithium diisopropylamide, prepared from diisopropylamine (77.0 mg, 0.76 mmol) and *n*-butyllithium (0.30 mL, 0.76 mmol, 2.5 M in hexane), was dissolved in THF (3 mL) and cooled to −78 °C. HMPA (149 mg, 0.83 mmol) was added, and the mixture stirred for 20 min. A solution of (*E*)- and (*Z*)-(1*R*,6*S*,7*S*)-4-(bromocarbethoxymethylidene)-1-methyl-7-isopropylbicyclo[4.3.0]nonane (**10**) (237.1 mg, 0.69 mmol) in THF (3 mL) was then added dropwise via cannula. Stirring was continued at −78 °C for 1.5 h. Enone **23** (103.7 mg, 0.69 mmol) in THF (2 mL) was added, and the reaction quenched at −78 °C after 0.5 h with saturated NH_4Cl solution (4 mL) and ethyl ether (6 mL). The organic layer was washed with 3 N HCl (3 mL), and the combined aqueous layer was extracted with ethyl ether (3 × 5 mL). The organic layer was then washed with 3 N HCl (3 mL), and the combined aqueous layer was extracted with ethyl ether (3 × 5 mL). The organic layer was then washed with brine (3 × 4 mL) and dried (Na_2SO_4), and the solvents were removed in vacuo to yield vinylcyclopropanes **31-exo** and **31-endo** (endo:exo = 3:2) that were separated by column

chromatography (hexane/ether), 4:1) to give 63.4 mg (22%) of the exo isomer and 97.4 mg (34%) of the endo isomer. **31-exo**: R_f = 0.47 (hexane/ether, 4:1); IR (neat) 2950, 2870, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (s, 3 H), 0.80 (d, 3 H, J = 7.0 Hz), 0.88 (d, 3 H, J = 7.0 Hz), 1.00 (d, 3 H, J = 7.0 Hz), 1.15 (s, 3 H), 1.20 (t, 3 H, J = 7.0 Hz), 1.05–2.30 (m, 18 H), 2.39 (m, 1 H), 4.08 (m, 2 H), 5.57 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.1 (CH_3), 14.2 (CH_3), 17.8 (CH_3, double intensity), 18.7 (CH_3), 21.6 (CH_3), 24.8 (CH_2, double intensity), 30.5 (CH), 33.8 (CH_2, double intensity), 38.9 (CH_2), 40.3 (C), 41.1 (CH_2, double intensity), 41.1 (CH), 42.3 (C), 45.6 (C), 46.9 (CH), 47.3 (CH, double intensity), 53.9 (C), 60.7 (CH_2), 128.9 (CH), 132.2 (C), 169.1 (C), 215.7 (C); MS (70 eV, rel intensity), m/e 412.2 (30, M^+), 384.3 (8), 339.3 (10), 315.2 (9), 159.1 (7), 123.1 (22). Calcd for $C_{27}H_{40}O_3$: 412.2977. Found: 412.2976. **31-endo**: R_f = 0.19 (hexane/ether, 4:1); IR (neat) 2970, 2890, 1730, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.65 (s, 3 H), 0.79 (d, 3 H, J = 7.0 Hz), 0.88 (d, 3 H, J = 7.0 Hz), 1.00 (d, 3 H, J = 7.0 Hz), 1.02 (s, 3 H), 1.20 (t, 3 H, J = 7.0 Hz), 1.10–1.88 (m, 10 H), 1.88–2.28 (m, 9 H), 4.09 (q, 2 H, J = 7.0 Hz), 5.80 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.8 (CH_3), 14.0 (CH_3), 18.3 (CH_3), 18.7 (CH_3, double intensity), 21.7 (CH_3), 24.7 (CH_2, double intensity), 30.4 (CH), 30.7 (CH_2), 33.3 (CH_2), 38.7 (CH_2), 39.9 (C), 41.0 (CH_2), 41.8 (CH_2), 42.1 (CH), 42.3 (C), 44.5 (C), 47.1 (CH, double intensity), 47.2 (CH), 52.5 (C), 61.1 (CH_2), 131.0 (CH), 131.1 (C), 169.9 (C), 214.8 (C); MS (70 eV, rel intensity), m/e 412 (100, M^+), 384 (18), 366 (12), 339 (35), 159 (15), 123 (30), 95 (35), 55 (62). Calcd for $C_{27}H_{40}O_3$: 412.2977. Found: 412.2991.

Ethyl [3*R*-(3α,3aα,5aβ,5bβ,6aβ,9α,9aα,11a*S)]-5-Oxo-2,3,3a,4,5,5a,5b,6,6a,7,8,9,9a,10-tetradecahydro-3,5a,6a-trimethyl-9-isopropyl-1*H*-pentaleno[1,6*a*-*a*]-*s*-indacene-11-carboxylate (40a and 5b Epimer 40b).** Vinylcyclopropane **31** (55.6 mg, 0.14 mmol) was pyrolyzed at 585 °C and 10^{-4} mmHg according to the general procedure to yield 44.5 mg of a 1:1 mixture (75% by GC) of **40a** and **40b**. This mixture was separated by chromatography on silica gel (hexane/ether, 9:1) to give 13.3 mg (24%) of **40a** and 15.2 mg (27%) of **40b**. **40a**: R_f = 0.58 (hexane/ether, 4:1); $[\alpha]_D$ +75° (c 0.27, $CDCl_3$); IR (neat) 2930, 2850, 1725, 1700, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (d, 3 H, J = 7.0 Hz), 0.80 (s, 3 H), 0.88 (d, 3 H, J = 7.0 Hz), 0.96 (d, 3 H, J = 7.0 Hz), 1.05 (s, 3 H), 1.30 (t, 3 H, J = 7.0 Hz), 1.15–2.08 (m, 15 H), 2.20 (m, 2 H), 2.42 (dd, 1 H, J_1 = 12.0, J_2 = 7.2 Hz), 2.55 (dd, 1 H, J_1 = 12.0, J_2 = 4.8 Hz), 3.38 (dd, 1 H, J_1 = 15.0, J_2 = 4.8 Hz), 4.21 (dq, 2 H, J_1 = 7.0, J_2 = 3.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 17.3 (CH_3), 18.2 (CH_3), 18.3 (CH_3), 21.8 (CH_3), 22.1 (CH_3), 24.6 (CH_2), 27.9 (CH_2), 29.7 (CH), 30.8 (CH_2), 34.4 (CH_2), 38.5 (CH_2), 40.6 (CH), 41.8 (CH_2, double intensity), 42.1 (C), 46.3 (CH), 50.4 (CH, double intensity), 55.2 (CH), 56.7 (C), 59.7 (CH_2), 69.2 (C), 129.4 (C), 156.5 (C), 165.8 (C), 221.6 (C); MS (70 eV, rel intensity), m/e 412 (30, M^+), 384 (15), 366 (5), 339 (20), 223 (9), 149 (100), 123 (50), 57 (45). Calcd for $C_{27}H_{40}O_3$: 412.2977. Found: 412.2931. **40b**: R_f = 0.47 (hexane/ether, 4:1); IR (neat) 2930, 2840, 1725, 1700 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (s, 3 H), 0.82 (d, 3 H, J = 6.0 Hz), 0.85 (d, 3 H, J = 6.0 Hz), 0.96 (s, 3 H), 1.02 (d, 3 H, J = 7.0 Hz), 1.30 (t, 3 H, J = 7.0 Hz), 1.00–1.94 (m, 12 H), 1.94–2.70 (m, 7 H), 3.12 (t, 1 H, J = 9.0 Hz), 4.20 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 16.1 (CH_3), 18.9 (CH_3), 19.2 (CH_3), 21.5 (CH_3), 23.0 (CH_3), 26.2 (CH_2), 30.9 (CH), 31.2 (CH_2), 32.1 (CH_2), 35.2 (CH_2), 39.2 (CH_2), 39.4 (CH_2), 40.3 (CH_2), 42.7 (C), 43.3 (CH), 45.4 (CH), 47.3 (CH), 49.9 (CH), 50.2 (CH), 58.4 (C), 59.5 (CH_2), 68.4 (C), 131.1 (C), 163.0 (C), 165.0 (C), 226.1 (C); MS (70 eV, rel intensity), m/e 412.3 (25 M^+), 338.3 (100), 296.2 (42), 271.2 (40), 123.1 (72), 95.1 (50). Calcd for $C_{27}H_{40}O_3$: 412.2977. Found: 412.2972.

Ethyl [3*R*-(3α,3aα,5aβ,5bβ,6aβ,9α,9aα,11a*S)]-2,3,3a,4,5,5a,5b,6,6a,7,8,9,9a,10-Tetradecahydro-3,5a,6a-trimethyl-9-isopropyl-1*H*-pentaleno[1,6*a*-*a*]-*s*-indacene-11-carboxylate (62a).** Pentacyclic ketone **40a** (27.5 mg, 0.067 mmol) was dissolved in MeOH (1 mL), and $NaBH_4$ (10 mg, 0.27 mmol) was added at room temperature. The reaction was stirred for 20 min, quenched carefully with water (0.5 mL) and ethyl ether (1 mL), and acidified with 3 N HCl (0.5 mL). The aqueous layer was extracted with ethyl ether (3 × 0.5 mL), the combined organic layer was washed with brine (3 × 0.5 mL) and dried (Na_2SO_4), and the solvents were evaporated in vacuo to yield a mixture of alcohols (27 mg, 98%). **63a**: R_f = 0.48 and 0.28 (hexane/ether, 4:1); IR (neat) 3410, 2930, 2850, 1690, 1620 cm^{-1}. The alcohols were dissolved in 1 mL of THF and NaH (30 mg) (previously washed with 3 mL of THF), and one crystal of imidazole was added. The mixture was refluxed for 1 h, then CS_2 (1 mL) was added, and the mixture was refluxed for 30 min. Finally methyl iodide (1 mL) was added and the mixture refluxed for 30 min. The reaction was quenched *very* carefully with water (0.5 mL) and CH_2Cl_2 (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The organic layer was washed with brine (3 × 1 mL) and dried (Na_2SO_4), and the solvents were removed in vacuo. The crude xanthates were filtered through a plug of silica gel using hexane/ether (9:1) as the eluant. R_f = 0.77 (hexane/ether, 9:1). The xanthates were dissolved in toluene (1 mL), and the mixture was heated to reflux. *n*-Tributyltin hydride (27 mL) dissolved in 1 mL of toluene was added in portions (4 × 0.25 mL of solution), then AIBN (2 mg) was added, and the mixture was refluxed for 20 min. The solvent was evaporated in vacuo and the crude mixture chromatographed in hexane to give 12.4 mg (47% for alcohols **63a**) of **62a**: R_f = 0.61 (hexane/ether, 95:5); $[\alpha]_D$ −84° (c 0.17, $CDCl_3$); IR (neat) 2920, 2850, 1700, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (d, 3 H, J = 7.0 Hz), 0.81 (s, 3 H), 0.88 (d, 3 H, J = 6.0 Hz), 0.98 (d, 3 H, J = 6.0 Hz), 1.00 (s, 3 H), 1.05–1.15 (m, 2 H), 1.30 (t, 3 H, J = 7.0 Hz), 1.15–1.50 (m, 6 H), 1.50–1.90 (m, 11 H), 2.28 (dd, 1 H, J_1 = 15.6, J_2 = 6.0 Hz), 2.45 (dd, 1 H, J_1 = 12.0, J_2 = 6.0 Hz), 3.25 (dd, 1 H, J_1 = 15.6, J_2 = 4.8 Hz), 4.15 (q, 2 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3), 17.7 (CH_3), 18.4 (CH_3), 20.0 (CH_3), 21.8 (CH_3, double intensity), 24.7 (CH_2), 28.0 (CH_2), 29.8 (CH), 30.9 (CH_2, double intensity), 36.2 (CH_2), 38.2 (CH_2), 38.8 (CH_2), 39.1 (CH_2), 42.1 (C), 43.7 (CH), 46.7 (CH), 49.6 (CH), 52.0 (CH), 52.6 (C), 56.9 (CH), 59.4 (CH_2), 71.8 (C), 133.5 (C), 153.5 (C), 167.2 (C). MS (70 eV, rel intensity), m/e 398 (12, M^+), 369 (6), 325 (100), 231 (15), 221 (20), 188 (20), 177 (20), 158 (80). Calcd for $C_{27}H_{42}O_2$: 398.3184. Found: 398.3149.

Ethyl [3*R*-(3α,3aα,5aβ,5bα,6aβ,9α,9aα,11a*S)]-2,3,3a,4,5,5a,5b,6,6a,7,8,9,9a,10-Tetradecahydro-3,5a,6a-trimethyl-9-isopropyl-1*H*-pentaleno[1,6*a*-*a*]-*s*-indacene-11-carboxylate (62b).** By use of a procedure indential with that for the preparation of **62a**, pentacyclic ketone epimer **40b** (25.3 mg, 0.06 mmol) was converted to retigeranic acid ethyl ester epimer in 44% overall yield. R_f = 0.61 (hexane/ether, 95:5); IR (neat) 2940, 2860, 1705, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (s, 3 H), 0.82 (d, 3 H, J = 7.0 Hz), 0.88 (d, 3 H, J = 7.0 Hz), 0.93 (s, 3 H), 0.98 (d, 3 H, J = 7.0 Hz), 1.30 (t, 3 H, J = 7.0 Hz), 1.00–1.85 (m, 18 H), 2.10 (m, 1 H), 2.55 (m, 2 H), 2.75 (t, 1 H, J = 8.7 Hz), 4.19 (m, 2 H); MS (70 eV, rel intensity), m/e 398 (20, M^+), 384 (5), 369 (4), 325 (100), 135 (50), 57 (40); ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3), 14.4 (CH_3), 18.9 (CH_3), 19.2 (CH_3), 19.6 (CH_3), 21.6 (CH_3), 26.2 (CH_2), 30.0 (CH_2), 31.0 (CH_2, double intensity), 33.1 (CH), 36.7 (CH_2), 38.2 (CH_2, double intensity), 40.4 (CH_2), 42.6 (C), 42.8 (CH), 45.6 (CH), 47.6 (CH), 51.7 (CH), 52.6 (C), 58.0 (CH), 58.0 (CH_2), 71.3 (C), 134.3 (C), 150.0 (C), 167.1 (C). Calcd for $C_{27}H_{42}O_2$: 398.3184. Found: 398.3087.

Retigeranic Acid (11). Retigeranic acid ethyl ester (**62a**) (6.0 mg, 1.5 × 10^{-2} mmol) was dissolved in EtOH (1 mL), and 35 μL of a 5% aqueous KOH solution was added. The mixture was refluxed for 2 h, then the solvent was removed in vacuo, and the residue was dissolved in 0.5 mL of ethyl ether and 0.5 mL of 5% HCl. The aqueous layer was extracted with ether (2 × 0.5 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC to give 2.5 mg (45%) of retigeranic acid (**11**) identical in spectral and chromatographic properties with the natural sample. (We thank Profs. Paquette and Shibata for providing ^1H NMR and natural sample, respectively.) R_f = 0.54 (hexane/EtOAc, 4:1); $[\alpha]_D$ −98° (c 0.125, $CDCl_3$); ^1H NMR ($CDCl_3$) δ 0.78 (d, 3 H, J = 6.6 Hz), 0.83 (s, 3 H), 0.88 (d, 3 H, J = 6.7 Hz), 0.99 (s, 3 H), 0.99 (d, 3 H, J = 6.2 Hz), 1.00–1.92 (m, 19 H), 2.37 (dd, 1 H, J_1 = 14.6, J_2 = 6.9 Hz), 2.47 (dd, 1 H, J_1 = 11.5, J_2 = 6.3 Hz), 3.33 (dd, 1 H, J_1 = 16.0, J = 3.5 Hz), 8.69 (s, 1 H).

Epimerization of 62b to 62a. Epimer **62b** (1.5 mg, 3.8 × 10^{-3} mmol) was dissolved in CCl_4 (0.5 mL), and *N*-bromosuccinimide (2 mg, 11.3 × 10^{-3} mmol) and benzoyl peroxide (less than one crystal) were added. The reaction mixture was refluxed for 30 min, it was then filtered through a plug of cotton, and the solvent was removed. Absence of the starting epimer was demonstrated by GC analysis. The residue was dissolved in toluene (0.5 mL), and a solution of *n*-tributyltin hydride in toluene (36 μL) of a 100 mg/mL solution, 12.4 × 10^{-3} mmol) was added dropwise. The reaction was refluxed for 20 min; then the toluene was removed in vacuo. The crude reaction mixture was purified by preparative TLC (hexane, three elutions). The compound obtained was co-injected with epimer **62a**, and it had the same retention time. ^1H NMR showed the same pattern for the C-5b proton, but at 3.0 ppm instead.

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Supplementary Material Available: Experimental and spectral data for compounds **7**, **9**, **17a**, **20-exo**, **20-endo**, **24**, **25c**, **30-exo**, **30-endo**, **34**, **54**, **56**, **60a**, **60b**, **61a** (12 pages). Ordering information is given on any current masthead page.

Synthesis of the Heptacyclic Indole Alkaloid (±)-Kopsine and Related Studies

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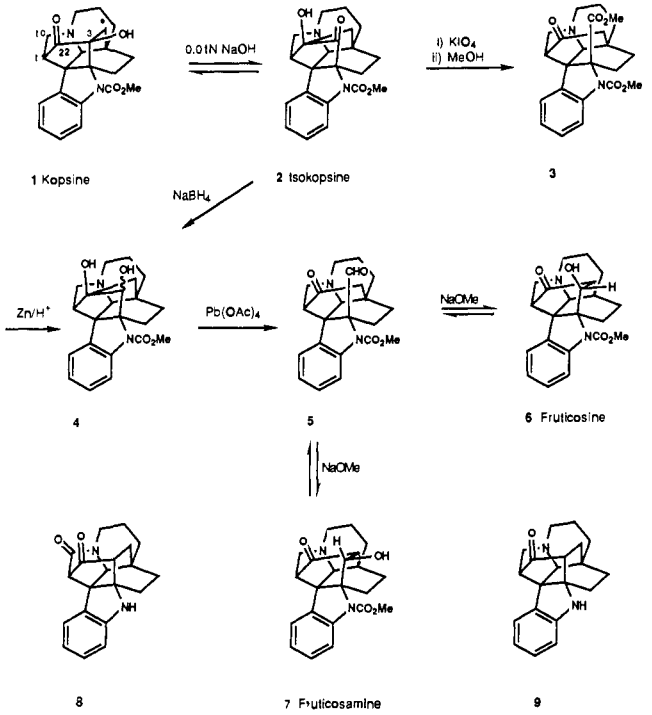
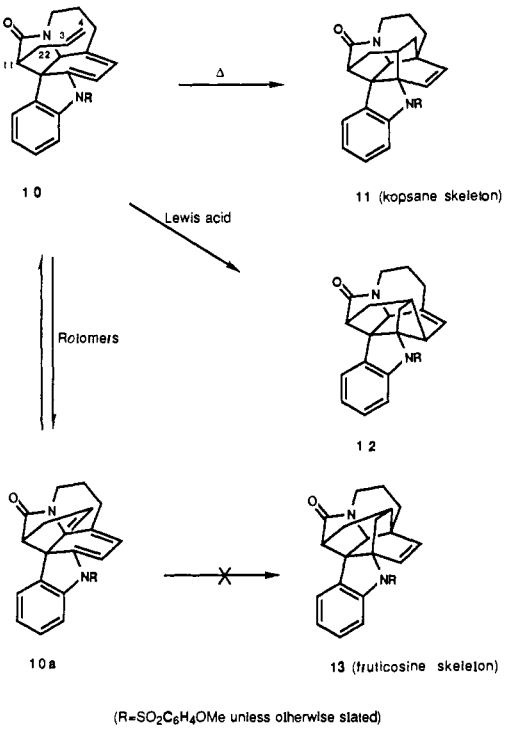
Abstract: The synthesis of the heptacyclic indole alkaloid kopsine (**1**) was achieved by starting with the homoannular diene **14**. Alkylation of the derived anion **15** with allyl bromide gave **16**, which was converted into N^1-[(*p*-methoxyphenyl)-sulfonyl]-10,22-dioxokopsane (**25**) as previously reported. Cleavage of the non-enolizable β-keto amide **25** with sodium hydroxide gave the acid **26**. The (*p*-methoxyphenyl)sulfonyl group was reductively removed and replaced by CO_2Me to give **27**. Reduction of **27** to the primary alcohol **28** followed by conversion to the *o*-nitrophenylselenide and oxidation gave the *exo*-methylene derivative **31**. Osmylation of **31** gave **32**, and Moffatt–Swern oxidation provided the α-hydroxy aldehyde **33**. Treatment of **33** with lithium diisopropylamide in THF at −78 °C gave the aldol product **34**. Diborane reduction of **34** gave the diol **35** after acidic workup. Moffatt–Swern oxidation of **35** gave kopsine (**1**).

Kopsine (**1**) was first isolated in 1890.[1] However, its complex heptacyclic structure was not determined until the early 1960s.[2] For many years, it was thought that **1** was a member of the *Strychnos* family of alkaloids, because of its similar biology.[3] **1** provides a structural correlation and synthetic link with another class of indole alkaloids known as the fruticosanes. In 0.01 N sodium hydroxide, **1** undergoes as α-ketol shift rearrangement to give isokopsine (**2**). Periodate fission of **2** gave **3**, which was



reduced with Zn/H_2SO_4 to give dihydroisokopsine (**4**). Sodium borohydride reduction of isokopsine (**2**) also gave dihydroisokopsine (**4**). Treatment of **4** with lead tetraacetate provided the keto aldehyde **5**, which undergoes aldol condensation leading to fruticosine (**6**) and fruticosamine (**7**) (cf. kopsine ⇌ isokopsine).[4]

Scheme I



(R=$SO_2C_6H_4OMe$ unless otherwise stated)

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