NMR ($CDCl_3$, 250 MHz) δ 2.66 (s, 3 H), 7.2–8.0 (m, 10 H), 8.98 (d, J = 8 Hz, 2 H), 9.96 (s, 1 H).

Pentaphen-5-ol Acetate (25). This compound was prepared from 0.75 g of **13a** in the same manner as **24** except that the reaction with DMAD was carried out for 8 days. Small amounts of TCAA were added daily after 4 days. To the final reaction mixture was added 150 mL of water. The resulting precipitate was filtered, air-dried, and chromatographed on silica gel, eluting with toluene. Removal of the solvent from the appropriate fractions and recrystallization from toluene–hexane gave **25** in 22% yield, mp 185–187 °C: IR (Nujol) 1757 (C=O), 1206, 1163, 1062, 873, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.65 (s, 3 H), 7.56–7.63 (m, 4 H), 7.63 and 7.70 (AB q, J = 9.5 Hz, 2 H, upfield portion obscured), 7.94–7.97 (m, 1 H), 8.01–8.05 (m, 1 H), 8.15–8.19 (m, 2 H), 8.27 (s, 1 H), 9.19 (s, 1 H), 9.24 (s, 1 H).

Anal. Calcd for $C_{24}H_{16}O_2$: C, 85.69; H, 4.79. Found: C, 85.46; H, 5.00.

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Registry No. **3a**, 34883-80-2; **3b**, 13102-93-7; **4a**, 92878-63-2; **4b**, 92878-64-3; **6a**, 113600-56-9; **6b**, 113600-57-0; **8a**, 113600-58-1; **8b**, 113600-59-2; **9a**, 113600-60-5; **9b**, 113600-61-6; **10**, 113600-62-7; **11**, 113600-63-8; **13a**, 4711-54-0; **13b**, 5060-75-3; **13c**, 53223-77-1; **14a**, 92878-65-4; **14b**, 92878-66-5; **14c**, 92878-67-6; **16a**, 113600-64-9; **16b**, 113600-65-0; **16c**, 113600-66-1; **18a**, 113600-67-2; **18b**, 113600-68-3; **18c**, 113600-69-4; **19a**, 113600-70-7; **19b**, 113600-71-8; **19c**, 113600-72-9; **20**, 113600-73-0; **21**, 113600-74-1; **22**, 113600-75-2; **23**, 41774-34-9; **24**, 63077-06-5; **25**, 113600-76-3; **37**, 113600-77-4; **38**, 113600-78-5; **39**, 113600-79-6; **41**, 113627-38-6; **42**, 113600-80-9; **43**, 113600-81-0; **44a**, 113600-82-1; **44b**, 113600-83-2; DMAD, 762-42-5; methyl acrylate, 96-33-3.

Type I Intramolecular Cycloadditions of Vinylketenes

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The scope of type I intramolecular [2 + 2] cycloadditions of alkenes with α,β-unsaturated ketenes (see eq 1) has been explored. These reactions generally produce bicyclo[3.2.0]heptan-6-ones containing an unsaturated substituent at position 5. Ketenes **4**, **7**, **13**, and **30** undergo the expected cycloaddition to give **5**, **8**, **14**, and **31** in 50–80% yield. Ketenes **10** and **16** undergo a 1,5-sigmatropic hydrogen shift to give dienals **11** and **17**. Ketenes **23** and **24** undergo a reversible electrocyclic ring closure instead of a cycloaddition to give cyclobutenones **25** and **26**. At higher temperatures electrocyclic ring closure is reversible and cyclobutenones **25** and **26** can be converted into **27** and **28** in 75% yield. Type I intramolecular cycloadditions cannot be used to produce bicyclooctanones such as **38**. These vinyl cyclobutanones are versatile synthetic intermediates. Treatment of **32** with potassium hydride gives **34** and **35**, suggesting that this approach will be useful for steroid synthesis. Treatment of **8** with boron trifluoride gives **39**.

Introduction

The stereospecific cycloaddition of ketenes to alkenes provides an attractive route to cyclobutanones and is one of the few general methods for carbofunctionalization of alkenes. We[1] and others[2] have recently recognized that the intramolecular version of this reaction provides a general method for the synthesis of polycyclic cyclobutanones. Although simple ketenes do undergo intramolecular [2 + 2] cycloaddition with some alkenes, satisfactory yields are not generally obtained unless activated ketenes are used.

Intramolecular [2 + 2] cycloadditions of alkenes with α,β-unsaturated ketenes proceed in mugh higher yield than with simple ketenes. The role of the double bond may be to either accelerate the cycloaddition and/or to retard oligomerization and other side reactions. These cycloadditions are particularly attractive since the resulting vinylcyclobutanones are versatile synthetic intermediates.[3-6] α,β-Unsaturated ketenes are versatile addends since the alkene containing side chain can be attached to the unsaturated ketene at either the ketene carbon (type I, eq 1),[1c,2e] the α-carbon (type II, eq 2),[1b,c,g,h,2c,g] or the β-carbon (type III, eq 3).[1a,c,2b] We report here a systematic study of the scope and limitations of type I reactions and an initial exploration of the reactivity of the adducts.[7]

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(4) (a) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943. (b) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

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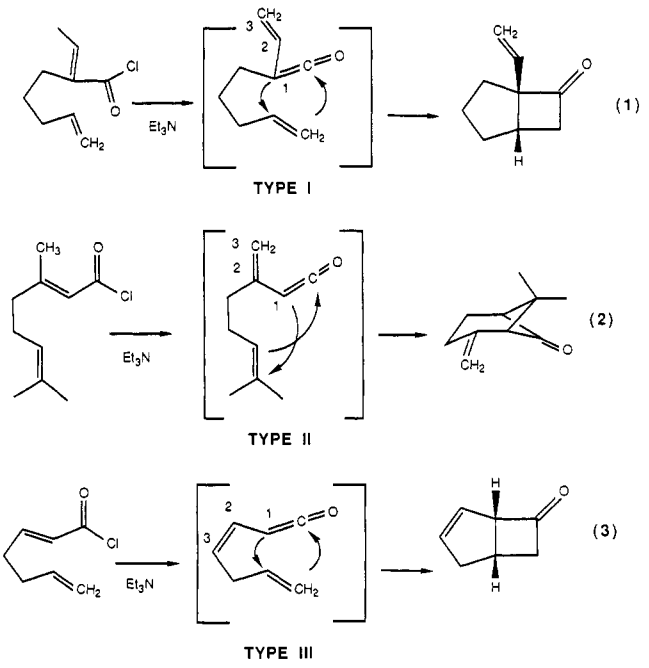
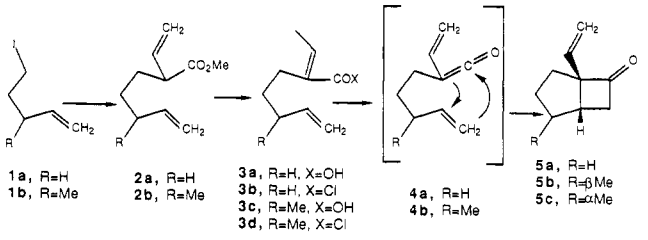


Results and Discussion

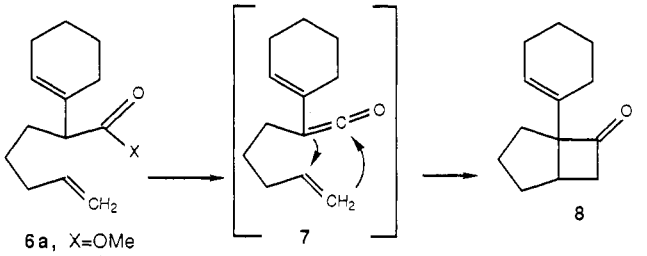
Cycloaddition of Ketene 4. Reaction of methyl crotonate with LDA in THF at −78 °C containing 1 equiv of HMPA gave the dienolate,[8] which was treated with 5-iodo-1-pentene (**1a**) to give ester **2a** in 65% yield. Hydrolysis of **2a** in 20% aqueous potassium hydroxide was accompanied by conjugation of the double bond to give the α,β-unsaturated acid **3a** in 96% yield. Acid **3a** was converted to the acid chloride **3b** by treatment with oxalyl chloride in benzene at 50 °C. The crude acid chloride was then added to excess triethylamine in toluene at reflux and the resulting solution was heated for 1.5 h to give the desired cycloadduct **5a**, via the presumed intermediacy of ketene **4a**, in 50% yield from **3a**.



Although many ketene cycloaddition reactions can be carried out at room temperature, reaction at 110 °C was shown to be necessary for optimal conversion of **3b** to **5a**. Reaction of **3b** with triethylamine in toluene at 60 °C for 2 h gave no **5a**. Reaction of **3a** with triethylamine in benzene at reflux for 2 h gave **5a** in ≈25% yield. The slow step is probably the cycloaddition of the keto ketene **4a** and not the conversion of the acylammonium salt to the ketene, since the literature precedent strongly suggests that **4a** should be formed readily at 60 °C.[9]

Bicycloheptanone **5b**, the 2-methyl homologue of **5a**, has been prepared by Gadwood and co-workers by a 12-step route and used as a key intermediate in an elegant synthesis of poitediol and dactyol.[6b] Bicycloheptanone **5b** can be prepared more easily by an intramolecular ketene–alkene [2 + 2] cycloaddition. 5-Iodo-3-methyl-1-pentene (**1b**), prepared from the alcohol via the mesylate in 61% overall yield, was added to the dienolate derived from methyl crotonate[8] to give **2b**. Hydrolysis of the crude ester in aqueous barium hydroxide at reflux gave acid **3c** in 78% yield from methyl crotonate. Conversion of **3c** to the acid chloride **3d** and thence to the ketene **4** as described above gave a 52% yield of a 2.5:1 mixture of **5b** and **5c**. The structures of the cycloadducts were unambiguously established by comparison with spectral data kindly provided by Dr. Gadwood.

Cycloaddition of Ketene 7. We next turned our attention to the preparation of substrates for type I intramolecular [2 + 2] ketene–alkene cycloadditions from more complex α,β-unsaturated esters. Alkylation of methyl 1-cyclohexeneacetate with **1a** followed by hydrolysis with aqueous barium hydroxide at reflux gave acid **6b** in 61% yield. Conjugation to the α,β-unsaturated acid does not occur during hydrolysis (vide infra). Conversion of **6b** to the acid chloride **6c** and thence to ketene **7** gave cycloadduct **8** in 68% overall yield.



1,5-Sigmatropic Hydrogen Shifts of Ketenes 10 and 16. Alkylation of the dienolate derived from ethyl (*E*)-2-hexenoate with **1a** followed by hydrolysis gave **9a** in 65% yield. The selective formation of the 3*Z* isomer in alkylation of 2*E* unsaturated esters has been demonstrated by Krebs[10a] and Kende.[10b] Conjugation of the double bond does not occur during hydrolysis. This is a kinetic rather than thermodynamic phenomenon since the α,β-unsaturated isomer is more stable in this case. Steric hindrance of the α-hydrogen will decrease the rate of conjugation. The increased lipophilicity of **9** as compared to **2** may cause **9** to aggregate in polar solvents which will also decrease the rate of conjugation. Conversion of **9b** to the acid chloride and thence to the ketene **10** proceeds normally. However, **10** does not undergo a cycloaddition but instead undergoes a 1,5-sigmatropic hydrogen shift to give dienal **11** in 64% yield from **9b** as a 5:1 mixture of 4*E* and 4*Z* isomers. The *Z* stereochemistry of the 2,3-double bond is assigned from the NMR absorptions of the aldehyde proton at δ 10.24 and 10.29, respectively. This value is typical for 2*Z* aldehydes.[11c] 2*E* aldehydes absorb at δ 9.4–9.5.[11c] The stereochemistry of the 4,5-double bond in the major isomer is assigned from the coupling constant of $J_{4,5}$, which is 14.3 Hz.

(7) For publication of a small portion of this work in preliminary form, see ref 1c.

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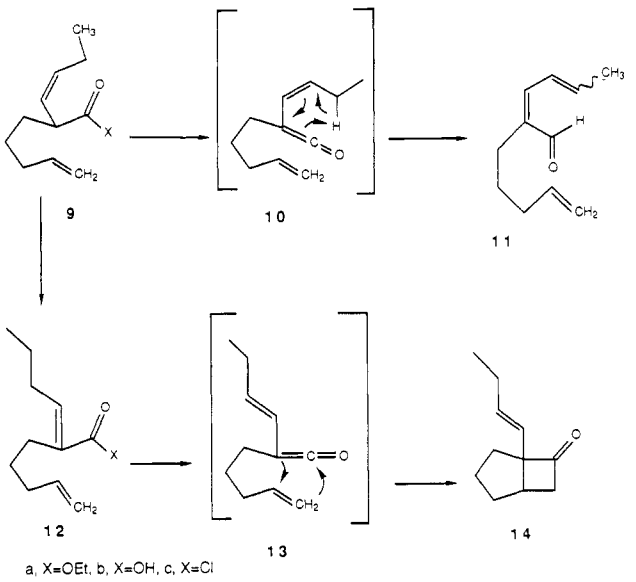
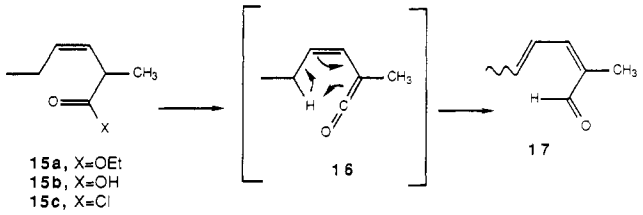
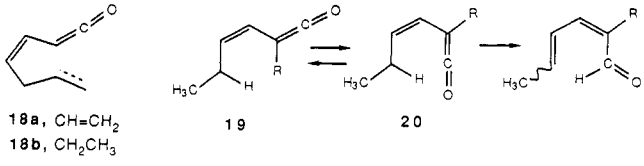


We have briefly explored the scope of this procedure for the synthesis of dienals. Alkylation[10] of ethyl (*E*)-2-hexenoate with methyl iodide followed by hydrolysis gave acid **15b**.[12] Conversion to the acid chloride **15c** and thence to the ketene **16** in benzene at reflux led to the expected rearrangement product **17** in 56% yield as a >10:1 mixture of 4*E* and 4*Z* isomers. Use of toluene at reflux for this reaction led to partial isomerization to the more stable 2*E* isomers.[11] This reaction may be useful for construction of the C-15 to C-20 segment of rifamycin S.[13]

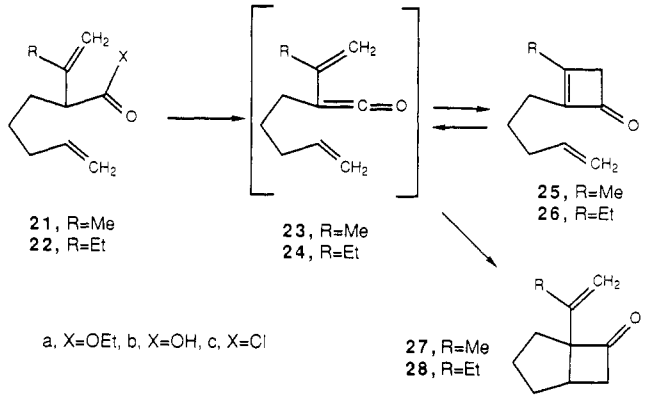


1,5-Sigmatropic hydrogen shifts of α,β-unsaturated ketenes have been observed only rarely at temperatures below 150 °C.[11,14] Interconversion of dienals and unsaturated ketenes does occur readily during flash vacuum pyrolysis.[11] We have not observed 1,5-sigmatropic hydrogen shifts in the reactions of corresponding *Z* α,β-unsaturated aldo ketenes generated by the same method. Ketene **18a** gives bicyclo[3.2.0]hept-3-en-6-one,[1c] while **18b** gives only oligomer. The additional substituent on the ketene carbon in keto ketenes facilitates the sigmatropic hydrogen shift by retarding oligomerization and, probably more importantly, by stabilizing the s-cis conformer **20** relative to the s-trans conformer **19**. Only the s-cis conformer **20** can undergo a 1,5-sigmatropic hydrogen shift.



Cycloaddition of Ketene 13. 1,5-Sigmatropic hydrogen shifts can occur only with α,β-unsaturated ketenes containing a β-substituent on the double bond cis to the ketene. We therefore set out to develop methods to convert **9a** to the trans ketene **13**. 1,4-Elimination of hydrogen chloride from **12c** should give only **13** and no **10** since the α-substituent forces the propyl group at the β-position to adopt an extended conformation. Conjugation of ester **9a** proved to be remarkably difficult. Success was finally achieved by heating crude **9a** with potassium ethoxide in *tert*-butyl alcohol for 3 days at reflux followed by addition of water to hydrolyze the ester to give **12b** in 62% overall yield. The use of *tert*-butyl alcohol as solvent was crucial since no conjugation occurred in ethanol, a more polar solvent where aggregation of nonpolar **9a** should be more pronounced.[15] Conversion of **12b** to acid chloride **12c** and thence to the ketene led selectively, as expected, to the trans ketene **13**, which reacted to give **14** in 52% yield from **12b**.

Electrocyclic Ring Closure and Cycloaddition of Ketenes 23 and 24. Unsaturated ketenes **23** and **24** demonstrate another alternative mode of reaction for α,β-unsaturated ketenes. Alkylation of ethyl 3,3-dimethylacrylate with **1a** followed by hydrolysis gave **21b** in 75% yield. Conversion to acid chloride **21c** and thence to ketene **23** with triethylamine in toluene at reflux for 3 h gave a 56% yield of cyclobutenone **25**. The interconversion of unsaturated ketenes and cyclobutenes is a well-known thermally allowed concerted reaction.[4b,16] It has often been used for the preparation of unsaturated ketenes. It is not generally suitable for the preparation of cyclobutenones. At higher temperatures the conversion of **23** to **25** is reversible and the reaction can be driven to the more stable bicycloheptanone **27**. Heating **25** for 4 days at 125–130 °C[4b] gave a 76% yield of **27**.



Electrocyclic ring closure of **23** to give **25** is faster than cycloaddition to give **27**. On the other hand, the cycloaddition is faster than ring closure for the closely related unsaturated ketenes **4**, **7**, and **13**. This difference in behavior could be due to (1) faster electrocyclic ring closure for **23** than for the other ketenes, (2) fast electrocyclic ring closure in all cases with slow electrocyclic ring opening for **25** only, or (3) slower cycloaddition for **23**. The available data support the first possibility. Treatment of **3b** with triethylamine at temperatures lower than 110 °C resulted in decreased yields of **5** and the recovery of hydrolyzed derivatives of **3b**. No cyclobutenone could be detected.

(12) Payne, G. B. *J. Org. Chem.* **1959**, *24*, 1830.
(13) (a) Rao, A. V. R.; Yadav, J. S.; Rao, C. S. *Tetrahedron Lett.* **1986**, *27*, 3297 and references cited therein. (b) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 2317.
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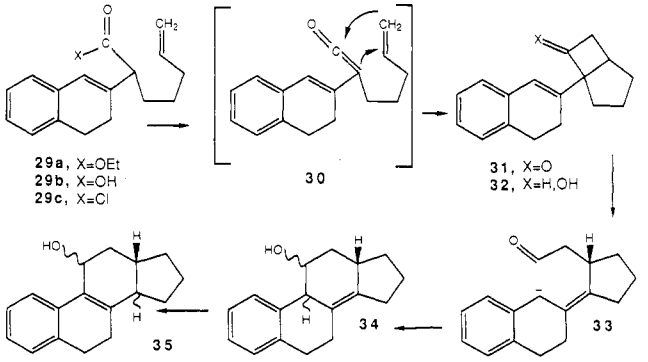
This suggests that cyclobutenones are not formed reversibly in the cycloadditions of **4**, **7**, and **13**. Treatment of **21c** with triethylamine in benzene at 40 °C for 2 h gave no **25**. Similar treatment at 60 and 80 °C gave complete conversion to **25**, strongly suggesting that the role of the α-substituent in **23** is to accelerate the electrocyclic ring closure.

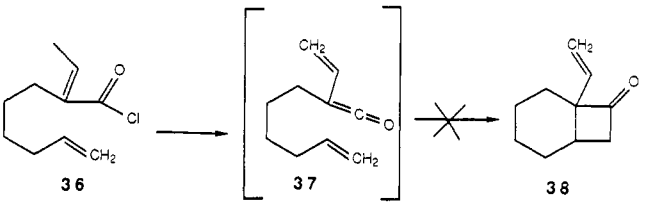
Electrocyclic ring closure occurs in good yield only with α,β-unsaturated ketenes containing a substituent on both the ketene and α-carbons and an unsubstituted β-carbon. Substituents on the ketene and α-carbon will perturb the equilibrium between the s-cis and s-trans conformers. Alkyl substituents at all three positions will perturb both the cycloaddition and electrocyclic ring closure due to electronic effects. Although the reasons for the perturbation of relative rates of cycloaddition and electrocyclic ring closure by alkyl substituents are obscure, the empirical rule fits all of the available data.

Regioselective deprotonation of β,β-disubstituted α,β-unsaturated esters can be used to prepare unsaturated ketenes for type I intramolecular [2 + 2] cycloadditions.[17] Alkylation of an 80:20 *E*/*Z* mixture of ethyl 3-methyl-2-pentenoate[18] with **1a** followed by hydrolysis gave **22b** contaminated with 10% of the double bond regioisomer obtained from deprotonation of the methylene carbon.[19] Conversion of **22b** to the acid chloride **22c** and thence to ketene **24** with triethylamine in toluene at reflux for 2 h gave **26** in 87% yield.[19] Heating **26** for 4 days at 130 °C at reflux gave **28**[19] in 75% yield.

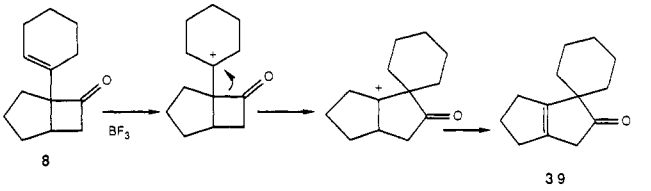
Cycloaddition of Ketene 30. Alkylation of ethyl 3,4-dihydronaphthalene-2-acetate[20] with **1a** gave **29a** in 75% yield, which was hydrolyzed to give **29b** in 87% yield. Conversion to the acid chloride **29c** and cyclization gave **31** in 81% yield.



Attempted Preparation of Bicyclo[4.2.0]octanones. Bicyclo[3.2.0]heptanones are produced readily in intramolecular ketene–alkene cycloadditions. Although bicyclo[4.2.0]heptanones can be produced from keteniminium salts and some classes of ketenes,[1,2] these reactions are not nearly as general. The longer tether decreases the rate of reaction by making the entropy of activation more negative. This allows dimerization and oligomerization to compete more effectively. Alkylation of methyl crotonate with 6-iodo-1-hexene followed by aqueous hydrolysis and treatment with oxalyl chloride gave acid chloride **36**. Treatment of **36** with triethylamine in toluene at reflux presumably generated the ketene **37**. However, cycloaddition to give **38** did not occur indicating that the type I intramolecular cycloadditions of α,β-unsaturated ketenes is not a general method for the synthesis of bicyclooctanones. In special cases where rotation of the tether is restricted this may be a viable method.



Reactions of Vinyl Cyclobutanones. Vinyl cyclobutanones are versatile intermediates, capable of rearrangement to cyclopentanes, cyclohexanes, or cyclooctanes under suitable conditions.[3-6] The development of these methodologies has been limited by the paucity of methods available for the synthesis of vinyl cyclobutanones. The intramolecular [2 + 2] cycloadditions described here provide an attractive method for the generation of these compounds and exploration of their rearrangements. Treatment of **8** in neat boron trifluoride etherate[5a] for 45 min at room temperature gave a 76% yield of the cyclopentanone **39**. The structure of **39** was determined by



analysis of its NMR spectra. The ^1H spectrum indicated that there were no olefinic protons. The ^{13}C spectrum demonstrated that there were two unsaturated carbons and that the structure was highly symmetrical since there were only seven hydrogen bearing carbons.

2-Vinylcyclobutanols undergo facile 1,3-sigmatropic rearrangements on treatment with base.[3b,c,4a] Rearrangement of **32** to give **34** should provide a very short approach to A-ring aromatic steroids. This rearrangement is more complex than those studied by Cohen[3b,c] and Danheiser.[4a] First, **34** can be formed as a mixture of four diastereomers because the cyclobutanol is part of a bicyclic system. Second, the presence of the aromatic ring stabilizes the intermediate **33**, facilitating the rearrangement and probably making ring closure of **33** to give **34** reversible.[21] Third, the rearrangement product **34** is an allylbenzene which can undergo base-catalyzed isomerization[22] to give the styrene **35**.

Reduction of **31** with sodium borohydride gave **32** in quantitative yield as a >19:1 mixture of diastereomers. Treatment of **32** with ≈4 equiv of potassium hydride in THF at 0 °C for 2 h gave a 70% yield of **34b** and a 20% yield of **34a**, two of the four diastereomers of **34**. Reaction of **34b** with a larger excess of KH in THF at 0 °C converted it cleanly into one of the four possible diastereomers of **35**. Alcohol **34a** does not isomerize to **35** under these conditions. These results suggest that interconversion of the stereoisomers of **34** by ring opening to give **33** is possible

(17) Alkylation occurs preferentially on the β-carbon syn to the ester and on the less substituted β-alkyl group. See: (a) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1985**, *26*, 1939; **1984**, *25*, 1333. (b) Majewski, M.; Green, J. R.; Snieckus, V. *Tetrahedron Lett.* **1986**, *27*, 531.

(18) DeBold, C. R.; Elwood, J. C. *J. Pharm. Sci.* **1981**, *70*, 1007.

(19) Deprotonation of the *E* isomer should occur exclusively on the methyl group which is both syn to the ester and kinetically more acidic. Deprotonation of the minor *Z* isomer will give a mixture since the ethyl group is syn to the ester while the methyl group is more acidic. The minor isomer formed by deprotonation of the ethyl group could not be separated and was carried on. Products derived from it appear as minor contaminants (≈10%) in **26** and **28**.

(20) Dauben, W. G.; Teranishi, R. *J. Org. Chem.* **1951**, *16*, 550.

(21) Wilson, S. R.; Mao, D. T. *Tetrahedron Lett.* **1977**, 2559.

(22) (a) Hubert, A. J.; Reimlinger, H. *Synthesis* **1969**, 97. (b) Moltrasio, G. Y.; Giacopello, D.; Vernengo, M. J. *Org. Prep. Proc. Int.* **1972**, *4*, 13.

and indicates that isomerization of **34** to **35** can occur under the reaction conditions.

Although the stereochemistry of **34** and **35** cannot be established from the available data, the gross structures are easily established by analysis of the ^{1}H NMR and UV spectra. The benzylic protons of **34a** and **34b** absorb at δ 3.3 and are coupled to the proton α to the alcohol, which absorbs at δ 4.27 and 4.45, respectively. Fairly weak absorptions at 265–270 nm ($\epsilon \approx$2000–3000) in the UV spectra are characteristic of tetralins.[23] On the other hand, no benzylic proton is observed in **35**, and the proton α to the alcohol absorbs downfield at δ 4.64 as a narrower peak. The UV spectrum shows a strong absorption at 264 nm (ϵ 11 177) characteristic of 1,2-dihydronaphthalenes.[23] We are continuing to explore the stereochemistry of the rearrangement of **32** to **34** and **35** and are developing methods for the introduction of the 18-methyl group and oxygen functionality at C-17 necessary for steroid synthesis.

Conclusion. The results presented here indicate that type I intramolecular cycloadditions of α,β-unsaturated ketenes to alkenes are a versatile method for the construction of synthetically useful bicyclo[3.2.0]heptanones. Competing 1,5-sigmatropic hydrogen shifts and electrocyclic ring closures are significant side reactions with certain classes of ketenes.

Experimental Section

Materials and Methods. NMR spectra were recorded on Varian EM-390 and XL-300 spectrometers in $CDCl_3$. Chemical shifts are reported in δ and coupling constants are reported in Hz. IR spectra were obtained on a Perkin-Elmer 683 spectrometer. Combustion analyses were performed by Spang and Galbraith Laboratories. All air-sensitive reactions were run under nitrogen in flame-dried glassware with magnetic stirring. Reagents were added via oven-dried syringes through septa. All solvents for air- or moisture-sensitive reactions were dried by standard procedures.

Methyl 2-Ethenyl-6-heptenoate (2a). *n*-Butyllithium (1.4 mL of 2.16 M in hexane, 3 mmol) was added dropwise to a solution of diisopropylamine (0.35 g, 3.5 mmol) in 10 mL of dry THF. The solution was stirred under nitrogen for 1 h at 0 °C and treated with HMPA (0.54 g, 3.0 mmol). The solution was stirred at 0 °C for an additional 0.5 h and cooled to −78 °C. Methyl crotonate (0.30 g, 3 mmol) in 5 mL of THF was added dropwise to the lithium diisopropylamide solution at −78 °C. The resulting solution was stirred under nitrogen for 1 h at −78 °C and treated with 5-iodo-1-pentene (**1a**) (0.60 g, 3.1 mmol) in 2 mL of dry THF. The reaction mixture was stirred at −78 °C for 2 h and warmed slowly to 25 °C. The reaction mixture was quenched with water (10 mL). Ether was added, and the organic layer was separated and washed with 10% hydrochloric acid (2 × 10 mL) and saturated brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give crude ester **2a**. Flash chromatography on silica gel gave 0.32 g (65%) of pure **2a**: ^{1}H NMR 5.6–6.1 (m, 2), 4.90–5.30 (m, 4), 3.70 (s, 3), 3.06 (dt, 1, J = 7.0, 7.0), 1.25–2.50 (m, 6); IR (neat) 1740 cm^{-1}.

(*E*)-2-Ethylidene-6-heptenoic Acid (3a). A mixture of **2a** (0.27 g, 1.6 mmol) and 10 mL of aqueous potassium hydroxide was heated at reflux overnight. The solution was extracted with ether and acidified with cold concentrated hydrochloric acid. The aqueous layer was extracted with ether, which was dried ($MgSO_4$) and evaporated to give 0.235 g (96%) of acid **3a**: ^{1}H NMR 7.02 (q, 1, J = 6.9), 5.83 (ddt, 1, J = 17.5, 10.5, 7.5) 5.03 (br d, 1, J = 17.5), 4.96 (br d, 1, J = 10.5), 2.32 (t, 2, J = 7.5), 2.08 (dt, 1, J = 7.5, 7.5), 1.83 (d, 3, J = 6.9), 1.52 (tt, 2, J = 7.5, 7.5); ^{13}C NMR 173.7, 140.4, 138.5, 137.6, 114.7, 33.6, 28.1, 25.6, 14.6; IR (neat) 2700–3500, 1683, 1640 cm^{-1}.

5-Ethenylbicyclo[3.2.0]heptan-6-one (5a). Oxalyl chloride (0.87 g, 6.8 mmol) was added to a solution of **3a** (0.185 g, 1.20 mmol) in 5 mL of benzene at 0 °C. The solution was warmed to room temperature and stirred for 1 h and then heated at 55 °C for 30 min. The solution was concentrated in vacuo to give the acid chloride **3b**. Acid chloride **3b** was dissolved in 10 mL of dry toluene and added to a solution of triethylamine (0.51 g, 5 mmol) in 15 mL of toluene at reflux. The solution was heated at reflux for 1.25 h, cooled, and filtered. The residue was washed with hexane and the combined organic layers were concentrated in vacuo to give crude **5a**. Purification by flash chromatography on silica gel (20:1 hexane–EtOAc) gave 81 mg (50%) of pure **5a**: ^{1}H NMR 5.94 (dd, 1, J = 10.8, 17.6), 5.22 (br d, 1, J = 17.6), 5.07 (br d, 1, J = 10.8), 3.24 (dd, 1, J = 9.8, 18.6), 2.75–2.85 (m, 1), 2.49 (dd, 1, J = 4.7, 18.6), 2.15 (dd, 1, J = 6.1, 13.0), 1.45–1.95 (m, 5); ^{13}C NMR 214.4, 135.9, 114.0, 78.3, 49.2, 36.3, 35.3, 32.7, 25.1; IR (neat) 1775, 1630 cm^{-1}.

5-Iodo-3-methyl-1-pentene (1b). Mesyl chloride (10.5 g, 92 mmol) was added to 3-methyl-4-penten-1-ol (4.183 g, 42 mmol), triethylamine (6.31 g, 63 mmol), and 30 mL of dry methylene chloride at 0 °C. The mixture was warmed to 25 °C and stirred for 20 h. The reaction mixture was quenched with 10% HCl solution, the layers were separated, and the organic layer was added to 10% NaOH solution and stirred for 2 h. The layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated to give 6.750 g (91%) of the mesylate.

Sodium iodide (1.2 g, 7.9 mmol) was added to a solution of the mesylate (1.166 g, 6.5 mmol) in 20 mL of acetone. The mixture was warmed to 56 °C and stirred for 13 h. The reaction mixture was cooled to 25 °C, concentrated, taken up in ether, washed twice with water and once with sodium thiosulfate, dried (Na_2SO_4), and concentrated to give 0.932 g (68%) of iodide **1b**: ^{1}H NMR 5.60 (ddd, 1, J = 7, 10, 17), 5.02 (br d, 1, J = 17), 4.91 (br d, 1, J = 10), 3.08 (m, 2), 2.21 (br dq, 1, J = 7, 7), 1.8 (m, 2), 0.98 (d, 3, J = 7).

5-Methyl-2(*E*)-ethylidenehept-6-enoic Acid (3c). Methyl crotonate (1.6 g, 16.4 mmol) was converted to the dianion with lithium diisopropylamide in THF and HMPA as described above and treated with iodide **1b** (3.107 g, 14.8 mmol). Normal workup gave 2.666 g (99%) of crude ester **2b**. Barium hydroxide octahydrate (15 g, 50 mmol) and 140 mL of water were added to a flask containing crude ester **2b**. The mixture was warmed to 100 °C for 8 h and cooled to 25 °C. Workup gave crude **3c**. Flash chromatography on silica gel (98:2 hexane–EtOAc) gave 1.964 g (79%) of pure **3c**: ^{1}H NMR 7.00 (q, 1, J = 7.0), 5.73 (ddd, 1, J = 7.0, 10.0, 17.2), 5.01 (br d, 1, J = 17.2), 4.95 (br d, 1, J = 10.0), 2.31 (ddd, 1, J = 7.0, 7.0, 12.6), 2.25 (ddd, 1, J = 7.0, 7.0, 12.6), 2.15 (dddq, 1, J = 7.0, 7.0, 7.0, 7.0), 1.81 (d, 3, J = 7.0), 1.40 (m, 2), 1.02 (d, 3, J = 7.0); ^{13}C NMR 173.5, 144.2, 139.9, 133.0, 112.9, 38.0, 35.6, 24.0, 20.2, 14.4.

2-Methyl-5-ethenylbicyclo[3.2.0]heptan-6-one (5b and 5c). Sodium hydride (0.04 g, 1.0 mmol) was added to an airless flask. After flame-drying the flask, 8 mL of dry toluene was added, and the flask was cooled to 0 °C. The acid **3b** (0.165 g, 0.8 mmol) was added to the flask in 8 mL of toluene. After 5 min, oxalyl chloride (0.6 g, 4.6 mmol) was added to the solution. After the addition was complete, the reaction was warmed to 25 °C and stirred for 2 h. The reaction mixture was filtered under anhydrous conditions and the solvent was evaporated in vacuo to give **3d**. Acid chloride **3d** was added in 30 mL of toluene over 30 min to a boiling solution of triethylamine (1.0 g, 10.0 mmol) in 150 mL of toluene. The solution was heated at 110 °C for 3.25 h. The solution was cooled to 25 °C, the solvent was evaporated at 20 Torr and 0 °C, and the resulting gum was dissolved in pentane, filtered through Celite, and evaporated to give 0.231 g of crude oil. The product was evaporatively distilled from 15 to 1 Torr at 25 °C to give 0.076 g (65%) of a ≈80% pure 2.5:1 mixture of **5b** and **5c**. Medium-pressure chromatography on silica gel (99.5:0.5 pentane–ether) gave 0.061 g (52%) of pure **5b** and **5c**. Initial fractions contained a 5:1 mixture of **5c** and **5b**; later fractions contained pure **5b**.

The data for **5b** are identical with those described by Gadwood et al.[6b]

The data for **5c**: ^{1}H NMR 5.92 (dd, 1, J = 10.4, 17.3), 5.08 (dd, 1, J = 1.1, 17.3), 4.98 (dd, 1, J = 1.1, 10.4), 2.96 (dd, 1, J = 10.5, 19.0), 2.71 (m, 1), 2.30 (m, 1), 2.11 (m, 1), 1.88 (m, 1), 1.61 (ddd, 1, J = 6.5, 12.5, 12.5), 1.41 (ddd, 1, J = 6.5, 12.5, 12.5), 1.28 (m, 1), 1.02 (d, 3, J = 7); ^{13}C NMR 213.9, 136.1, 113.8, 78.1, 43.1, 39.9, 37.2, 35.5, 32.5, 15.1; IR (neat) 1770, 1630, 1450, 1370, 1060, 990,

(23) Scott, A. I. *Interpretation of the Ultraviolet Spectra of Natural Products*; Pergamon: Oxford, 1964; Chapter 3.

905 cm^{-1}. The ^1H NMR spectrum is identical with that provided by Dr. Gadwood.

α-(4-Pentenyl)-1-cyclohexeneacetic Acid (6b). *n*-Butyllithium (1.6 mL of 2.2 M in hexane, 3.5 mmol) was added dropwise to a solution of diisopropylamine (0.49 mL, 3.5 mmol) in 10 mL of dry THF. The solution was stirred under nitrogen for 1 h at 0 °C and treated with HMPA (0.52 mL, 3.0 mmol). The solution was stirred at 0 °C for an additional 0.5 h and cooled to −78 °C. Methyl 1-cyclohexeneacetate (0.48 g, 3.1 mmol) in 2 mL of THF was added dropwise to the lithium diisopropylamide solution at −78 °C. The resulting solution was stirred under nitrogen for 1 h at −78 °C and treated with **1a** (0.60 g, 3.1 mmol) in 2 mL of dry THF. The reaction mixture was stirred at −78 °C for 2 h and warmed slowly to 25 °C. The reaction mixture was quenched with water (10 mL). Ether was added, and the organic layer was separated, washed with 10% hydrochloric acid (2 × 10 mL) and saturated brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give 0.67 g (99%) of crude ester **6a**, which was about 85% pure as determined by TLC and NMR analysis and was used without purification.

Crude ester **6a** (0.71 g, 3.2 mmol) was added to a solution of $Ba(OH)_2{\cdot}8H_2O$ (2.0 g, 6.3 mmol) in 30 mL of water. The solution was heated under reflux for 12 h. The solution was cooled, acidified with 10% hydrochloric acid, and extracted with diethyl ether (3 × 10 mL). The combined ether fractions were washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated to give crude acid. Flash chromatography on silica gel (4:1 hexane–EtOAc) gave 0.41 g (61.5%) of pure acid **6b** as a light yellow oil: ^1H NMR 11.15–11.48 (br s, 1), 5.78 (ddt, 1, J = 16.8, 10.0, 6.6), 5.63 (br s, 1), 5.00 (br d, 1, J = 16.8), 4.95 (br d, 1, J = 10.0) 2.91 (t, 1, J = 7.6), 1.96–2.15 (m, 6), 1.72–1.82 (m, 1), 1.51–1.67 (m, 5), 1.35–1.41 (m, 2); ^{13}C NMR 180.7, 138.4, 134.4, 125.6, 114.7, 53.1, 33.5, 29.1, 26.7, 25.9, 25.3, 22.8, 22.2; IR (neat) 2800–3200, 2930, 1700, 1640 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.09; H, 9.64.

5-(1-Cyclohexenyl)bicyclo[3.2.0]heptan-6-one (8). A solution of acid **6b** (0.525 g, 2.54 mmol) was added to a suspension of hexane-washed sodium hydride (0.068 g, of 60% dispersion in mineral oil, 2.82 mmol) in 3 mL of anhydrous benzene under nitrogen at 0 °C. The mixture was stirred for 10 min and treated with oxalyl chloride (1.746 g, 13.75 mmol) at 0 °C. The reaction mixture was allowed to warm to 25 °C slowly and then heated 55–60 °C for 1 h. The reaction mixture was cooled and evaporated in vacuo. The resulting acid chloride **6c** was taken up in 2 mL of toluene and added via syringe to a solution of triethylamine (2 mL, 14.33 mmol) in 10 mL of toluene at reflux under nitrogen. The bright yellow reaction mixture was heated at reflux for 3 h, cooled, and filtered through Celite. The residue was washed with ether and the combined filtrates were concentrated to give 0.464 g (97%) of crude product. Flash chromatography on silica gel (24:1 hexane–EtOAc) gave 0.325 g (68%) of pure **8**: ^1H NMR 5.59–5.65 (m, 1), 3.18 (dd, 1, J = 18.3, 10.1), 2.82–2.91 (m, 1), 2.41 (dd, 1, J = 18.3, 4.5), 1.97–2.13 (m, 4), 1.78–1.97 (m, 4), 1.49–1.78 (m, 6); ^{13}C NMR 215.3, 134.5, 120.5, 81.1, 49.2, 35.4, 33.3, 32.8, 25.8, 25.1, 25.0, 22.8, 22.2; IR (neat) 2930, 2860, 2840, 1770, 1670 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.05; H, 9.52.

2-((*Z*)-1-Butenyl)-6-heptenoic Acid (9b). Ethyl (*E*)-2-hexenoate (1.994 g, 14.04 mmol) was converted to the dienolate with lithium diisopropylamide in THF and HMPA as described above and treated with **1a** (1.871 g, 9.5 mmol). Normal workup gave 1.779 g (88%) of crude **9a**, which was estimated to be 80% pure and was hydrolyzed without purification.

Crude ester **9a** (1.778 g, 8.466 mmol) was hydrolyzed as described above to give crude **9b**. Flash chromatography on silica gel (4:1 hexane–EtOAc) gave 1.010 g (65%) of acid **9b**: ^1H NMR 12.11 (br s, 1), 5.77 (ddt, 1, J = 17.1, 10.3, 6.9), 5.57 (dt, 1, J = 10.7, 7.3), 5.31 (ddt, 1, J = 10.7, 9.8, 1.5), 4.99 (br d, 1, J = 17.1), 4.95 (br d, 1, J = 10.3), 3.33 (dt, 1, J = 9.8, 7.3), 2.05–2.12 (m, 4), 1.72–1.89 (m, 1), 1.31–1.59 (m, 3), 0.98 (t, 3, J = 7.6); ^{13}C NMR 181.4, 138.2, 135.0, 126.0, 114.8, 43.6, 33.4, 32.0, 26.2, 20.9, 14.0; IR (neat) 2800–3200, 2940, 1710, 1640 cm^{-1}. Anal. Calcd $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.59; H, 10.03.

(2*Z*,4*E*)-2-(4-Pentenyl)-2,4-hexadienal (11). Acid **9b** (0.305 g, 1.68 mmol) was converted to acid chloride **9c** as described above. A solution of **9c** in 5 mL of toluene was added to a solution of triethylamine (2.3 mL, 16.4 mmol) in 20 mL of toluene at reflux under nitrogen. The mixture was heated at reflux for 1.5 h and worked up as described above to give 0.236 g of crude aldehyde. Flash chromatography on silica gel (24:1 hexane–EtOAc) gave 0.176 g (64%) of aldehyde **11** as a ≈5:1 mixture of 4*E* and 4*Z* isomers.

The data for the major isomer: ^1H NMR 10.24 (s, 1), 7.03 (ddq, 1, J = 14.3, 11.7, 1.6), 6.86 (d, 1, J = 11.7), 6.07 (dq, 1, J = 14.3, 7.2), 5.79 (ddt, 1, J = 17.0, 10.5, 6.9), 5.02 (br d, 1, J = 10.5), 4.96 (br d, 1, J = 17.0), 2.22 (t, 2, J = 7.5), 2.08 (dt, 2, J = 7.5, 7.5), 1.91 (br d, 3, J = 7.2), 1.54 (tt, 2, J = 7.5, 7.5); ^{13}C NMR 190.8, 145.8, 138.7, 138.3, 136.6, 124.6, 114.6, 33.3, 29.4, 28.0, 18.6; IR (neat) 2925, 2860, 1669, 1638 cm^{-1}.

Partial data for the minor isomer: ^1H NMR 10.29 (s, 1), 7.25 (br d, 1, J = 11).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 77.95; H, 9.78.

2(*E*)-Butylidene-6-heptenoic Acid (12b). Potassium ethoxide (0.200 g, 2.38 mmol) was added to a solution of crude ester **9a** (0.138 g, 0.657 mmol) in 3 mL of *t*-BuOH. The resulting suspension was heated at reflux for 3 days. Water (2 mL) was added to the mixture which was then heated at reflux for an additional 1 h. The reaction mixture was cooled, acidified with 10% hydrochloric acid, and extracted with several portions of diethyl ether. The ether layers were washed with brine, dried ($MgSO_4$), and concentrated to give 0.104 g of the conjugated acid **12b**. Flash chromatography on silica gel (4:1 hexane–EtOAc) gave 74 mg (62% overall) of pure **12b**: ^1H NMR 12.04–12.18 (br s, 1), 6.92 (t, 1, J = 7.6), 5.81 (ddt, 1, J = 17.1, 9.8, 6.9), 5.00 (br d, 1, J = 17.1), 4.94 (br d, 1, J = 9.8), 2.02–2.35 (m, 6), 1.25–1.79 (m, 4), 0.95 (t, 3, J = 7.5); ^{13}C NMR 173.8, 145.6, 138.4, 131.7, 114.6, 33.6, 30.7, 28.4, 25.9, 21.9, 13.9; IR (neat) 2960, 1690, 1640 cm^{-1}.

5-((*E*)-1-Butenyl)-bicyclo[3.2.0]heptan-6-one (14). Acid **12b** (0.212 g, 1.166 mmol) was converted to the acid chloride **12c** as described above. A solution of **12c** in 2 mL of toluene was added to a solution of triethylamine (1.64 mL, 11.7 mmol) in 10 mL of toluene at reflux. The solution was heated at reflux for 4 h and worked up as described above to give 0.261 g of crude product. Flash chromatography on silica gel (24:1 hexane–EtOAc) gave 0.099 g (52%) of pure cyclobutanone **14**: ^1H NMR 5.62 (ddd, 1, J = 16.1, 5.9, 5.5), 5.52 (d, 1, J = 16.1), 3.22 (dd, 1, J = 18.6, 9.8), 2.68–2.75 (m, 1), 2.46 (dd, 1, J = 18.6, 4.4), 1.98–2.14 (m, 3), 1.79–1.92 (m, 3), 1.62–1.75 (m, 1), 1.42–1.54 (m, 1), 0.97 (t, 3, J = 7.4); ^{13}C NMR 215.4, 131.7, 126.7, 77.4, 49.1, 36.7, 35.7, 32.7, 25.5, 25.1, 13.5; IR (neat) 2950, 2860, 1775 cm^{-1}; MS, m/z (relative intensity) 164 (2, M), 122 (87), 107 (19), 93 (100), 79 (29). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 78.05; H, 9.53.

2-Methyl-(*Z*)-3-hexenoic Acid (15b). Ethyl (*E*)-2-hexenoate (2.751 g, 19.4 mmol) was converted to the dienolate with lithium diisopropylamide in THF and HMPA as described above and treated with iodomethane (2.643 g, 18.6 mmol). Normal workup gave 1.76 g of crude **15a**, which was estimated to be 80% pure and was hydrolyzed without purification.

Crude ester **15a** (1.76 g) was hydrolyzed as described above to give crude **15b**. Flash chromatography on silica gel (4:1 hexane–EtOAc) gave 0.834 g (35%) of acid **15b**: ^1H NMR 11.27 (br s, 1), 5.52 (dtd, 1, J = 10.7, 7.4, 1.1), 5.37 (ddt, 1, J = 10.7, 9.3, 1.4), 3.45 (dqd, 1, J = 9.3, 6.7, 1.1), 2.10 (dq, 1, J = 7.4, 7.2), 1.26 (d, 3, J = 6.7), 0.99 (t, 3, J = 7.2); ^{13}C NMR 181.8, 134.1, 127.2, 37.9, 20.8, 17.9, 14.1; IR (neat) 2800–3400, 2970, 1712, 1658 cm^{-1}. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.53; H, 9.38.

(2*Z*,4*E*)-2-Methyl-2,4-hexadienal (17). Acid **15b** (0.312 g, 2.44 mmol) was converted to acid chloride **15c** as described above. A solution of **15c** in 2 mL of benzene was added to a solution of triethylamine (4 mL, 28.5 mmol) in 15 mL of benzene at reflux under nitrogen. The mixture was heated at reflux for 2 h and worked up as described above to give 0.217 g of crude aldehyde. Flash chromatography on silica gel (25:1 hexane–EtOAc) gave 0.150 g (56%) of **17** as a >10:1 mixture of 4*E* to 4*Z* isomers.[11c]

The data for the major isomer: ^1H NMR 10.27 (s, 1), 7.03 (ddq, 1, J = 14.3, 11.6, 1.6), 6.95 (d, 1, J = 11.6), 6.04 (dq, 1, J = 14.3, 6.8), 1.90 (d, 3, J = 6.8), 1.83 (br s, 3); ^{13}C NMR 190.5, 146.1, 138.4, 132.8, 124.6, 18.7, 16.2; IR (neat) 2950, 1675, 1635, 1440 cm^{-1}.

The data for the minor isomer: ^1H NMR 10.32 (s, 1), 7.26 (br d, 1, J = 12).

A similar reaction was run for 2 h in toluene at reflux. NMR analysis showed that a 2:12:1:6 mixture of 2Z,4Z, 2Z,4E, 2E,4Z, and 2E,4E isomers was formed as determined by the absorptions at δ 10.32, 10.26, 9.51, and 9.42, respectively.[11c] Partial data for the 2E,4E isomer: ^{1}H NMR 9.42 (s, 1), 6.82 (br d, 1, J = 11), 6.55 (ddq, 1, J = 11, 15, 1.3), 6.27 (dq, 1, J = 15, 6.7), 1.94 (dd, 3, J = 1.3, 6.7), 1.83 (s, 3).

2-(1-Methylethenyl)-6-heptenoic Acid (21b). Ethyl 3,3-dimethylacrylate (1.6 g, 12 mmol) was converted to the dienolate with lithium diisopropylamide in THF and HMPA as described above and treated with **1a** (2 g, 10 mmol). Normal workup gave 1.96 g of crude ester **21a**, which was hydrolyzed without purification.

The crude ester **21a** (1.96 g) was hydrolyzed as described above to give crude **21b**. Flash chromatography on silica gel (4:1 hexane–EtOAc) gave 1.26 g (75%) of **21b**: ^{1}H NMR 5.78 (ddt, 1, J = 16.9, 10.0, 6.9), 5.04 (br d, 1, J = 16.9), 4.99 (br d, 1, J = 10.0), 4.94 (d, 1, J = 1.6), 4.93 (d, 1, J = 1.6), 3.05 (t, 1, J = 7.6), 2.09 (m, 2), 1.86 (m, 1), 1.78 (br s, 3), 1.62 (m, 1), 1.38 (m, 2); ^{13}C NMR 180.3, 141.9, 138.3, 114.8, 114.5, 52.8, 33.4, 29.2, 26.6, 20.1; IR (neat) 3200–2800, 2935, 1705, 1640 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.66.

Ethyl 2-(1-Ethylethenyl)-6-heptenoate (22a). Ethyl 3-methyl-2-pentenoate[18] (1.76 g, 12.4 mmol, 4:1 E/Z) in 5 mL of THF was converted to the dienolate with lithium diisopropylamide in THF and HMPA as described above and treated with 5-iodo-1-pentene (2.68 g, 13.7 mmol). Normal workup gave 2.47 g of crude material. Flash chromatography on neutral silica gel of 2.29 g (23:1 hexane–EtOAc) gave 1.686 g (70%) of **22a**: ^{1}H NMR 5.78 (ddt, 1, J = 6.7, 10.4, 17.2), 4.96 (m, 4), 4.13 (q, 2, J = 7.1), 2.98 (t, 1, J = 7.6), 2.06 (m, 4), 1.82 (m, 1), 1.60 (m, 1), 1.35 (m, 2), 1.24 (t, 3, J = 7.1), 1.05 (t, 3, J = 7.5); ^{13}C NMR 173.8, 148.4, 138.3, 114.6, 110.5, 60.3, 52.1, 33.5, 30.3, 27.2, 26.8, 14.1, 12.0; IR ($CDCl_3$) 2950, 1720 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.20; H, 10.51.

The ^{1}H NMR spectrum indicated that 5–10% of the regioisomer formed by deprotonation of the methylene carbon was present.

2-(1-Ethylethenyl)-6-heptenoic Acid (22b). Pure ester **22a** (0.589 g, 2.80 mmol) in 35 mL of t-BuOH was added to 0.395 g (9.85 mmol) of NaOH in 4 mL of water. The mixture was heated at reflux for 3 days. It was then cooled to 0 °C and acidified with aqueous 10% HCl. The solution was extracted with ether, and then the combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The brown oily residue was taken up in ether and filtered through a short column of Florisil. Evaporation in vacuo gave 0.510 g (100%) of pure **22b**: ^{1}H NMR 5.79 (ddq, 1, J = 6.9, 10.0, 17.0), 4.97 (m, 4), 3.03 (t, 1, J = 7.6), 2.09 (m, 4), 1.84 (m, 1), 1.63 (m, 1), 1.40 (m, 2), 1.06 (t, 3, J = 7.3); ^{13}C NMR 179.0, 147.9, 138.3, 114.8, 111.3, 51.9, 33.5, 30.1, 27.3, 26.8, 12.0; IR ($CDCl_3$) 3200–2500, 2950, 1740 (sh), 1700, 1640 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.55; H, 10.01.

The ^{1}H NMR spectrum indicated that 5–10% of the regioisomer formed by deprotonation of the methylene carbon was present.

3-Methyl-2-(4-pentenyl)-2-cyclobutenone (25). Acid **21b** (0.406 g, 2.42 mmol) was converted to the acid chloride **21c** as described above. A solution of **21c** in 2 mL of toluene was added to a solution of triethylamine (3.4 mL, 24.2 mmol) in 15 mL of toluene at reflux. The mixture was heated at reflux for 3 h and worked up as described above to give 0.339 g of crude **25**. Flash chromatography on silica gel (45:2 hexane–EtOAc) gave 0.202 g (56%) of pure **25**: ^{1}H NMR 5.77 (ddt, 1, J = 17.3, 10.2, 6.9), 5.00 (br d, 1, J = 17.3), 4.95 (br s, 1, J = 10.2), 3.09 (s, 2), 2.18 (s, 3), 2.02–2.09 (m, 4), 1.55–1.65 (m, 2); ^{13}C NMR 189.9, 168.9, 148.2, 137.8, 114.8, 51.0, 33.2, 26.0, 22.6, 15.5; IR (neat) 2940, 1758, 1640 cm^{-1}; MS, m/z (relative intensity) 135 (5, M – 15), 122 (100), 108 (40), 107 (54), 93 (42), 79 (58), 67 (58).

3-Ethyl-2-(4-pentenyl)-2-cyclobutenone (26). Acid **22b** (135 mg, 0.748 mmol) was converted to the acid chloride **22c** as described above. A solution of **22c** in 5 mL of toluene was added to a solution of NEt_3 (0.63 mL, 4.49 mmol) in 20 mL of toluene at reflux. The mixture was heated at reflux for 2 h and was worked up as described above to give 0.161 g of crude **26** containing some toluene. Flash chromatography (9:1 pentane–ether) of 130 mg gave 87.1 mg (87%) of **26**: ^{1}H NMR 5.80 (ddt, 1, J = 6.8, 10.3, 17.3), 4.97 (m, 2), 3.08 (br s, 2), 2.55 (q, 2, J = 7.5), 2.07 (m, 4), 1.60 (tt, 2, J = 7, 7), 1.19 (t, 3, J = 7.5); ^{13}C NMR 190.0, 173.7, 147.0, 138.0, 114.9, 48.9, 33.4, 26.4, 23.1, 22.8, 10.7; IR ($CDCl_3$) 2950, 1750, 1640 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.40; H, 9.40.

The ^{1}H NMR spectrum suggested that 10% of 3,4-dimethyl-2-(4-pentenyl)-2-cyclobutenone was present: ^{1}H NMR 3.35 (br q, 1, J = 7). This would be formed from the isomeric β,γ-unsaturated acid present in **22b**.

5-(1-Methylethenyl)bicyclo[3.2.0]heptan-6-one (27). Cyclobutenone **25** (0.166 g, 1.11 mmol) in 2 mL of dry toluene was heated in a sealed tube for 4 days at 125–130 °C. The solution was cooled and concentrated in vacuo to give crude **27**. Flash chromatography on silica gel (19:1 hexane–EtOAc) gave 0.126 g (76%) of pure **27**: ^{1}H NMR 4.90 (br s, 1), 4.78 (br s, 1), 3.21 (dd, 1, J = 18.2, 10.0), 2.85–2.94 (m, 1), 2.45 (dd, 1, J = 18.2, 4.5), 2.07–2.18 (m, 1), 1.78 (s, 3), 1.49–1.94 (m, 5); ^{13}C NMR 206.4, 142.7, 109.4, 81.5, 49.3, 35.9, 34.0, 32.9, 25.3, 20.2; IR (neat) 2942, 2860, 1770, 1640 cm^{-1}.

5-(1-Ethylethenyl)bicyclo[3.2.0]heptan-6-one (28). Cyclobutenone **26** (47.0 mg) in 8 mL of benzene was heated in a sealed tube under N_2 at 135 °C for 6 days. Evaporation in vacuo gave 44.1 mg of crude **28**, which was purified by flash chromatography on silica gel (29:1 hexane–EtOAc) to give 35.1 mg (74.7%) of **28**: ^{1}H NMR 4.99 (br s, 1), 4.80 (br s, 1), 3.20 (dd, 1, J = 9.7, 18.3), 2.86 (m, 1), 2.44 (dd, 1, J = 4.1, 18.3), 1.5–2.2 (m, 8), 1.06 (t, 3, J = 7.3); ^{13}C NMR 148.0, 106.9, 81.5, 49.2, 36.5, 34.1, 32.8, 25.8, 25.5, 12.0 (the carbonyl carbon was not observed); IR ($CHCl_3$) 2960, 1765 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.60; H, 8.89.

The ^{1}H NMR spectrum showed that 10% of the isomer containing a 1-methyl-1-propenyl substituent on the bicyclic framework was present: ^{1}H NMR 5.47 (br q, 1, J = 7), 2.41 (dd, 1, J = 4, 18).

α-(4-Pentenyl)-3,4-dihydronaphthalene-2-acetic Acid (29b). Ethyl 3,4-dihydronaphthalene-2-acetate[20] (2.323 g, 10.75 mmol) was converted to the dienolate with lithium diisopropylamide in THF and HMPA as described above and treated with **1a** (1.93 g, 9.84 mmol). Normal workup gave 2.88 g of crude **29a**. Flash chromatography on silica gel (23:2 hexane–EtOAc) gave 2.09 g (75%) of **29a**.

The purified ester **29a** (1.627 g, 5.73 mmol) was hydrolyzed as described above to give crude acid. Flash chromatography on silica gel (19:1 hexane–EtOAc) gave 1.27 g (87%) of **29b**: ^{1}H NMR 9.79 (br s, 1), 7.07–7.13 (m, 4), 6.39 (s, 1), 5.76 (ddt, 1, J = 16.8, 10.3, 6.5), 5.01 (br d, 1, J = 16.8), 4.95 (br d, 1, J = 10.3), 3.40 (m, 1), 3.18 (t, 1, J = 7.6), 2.80 (m, 1), 2.32 (m, 2), 2.09 (m, 2), 1.91 (m, 1), 1.70 (m, 1), 1.42 (m, 2); ^{13}C NMR 179.6, 138.1, 134.7, 127.1, 126.9, 126.4, 126.1, 126.0, 125.9, 125.8, 114.8, 52.5, 33.4, 29.0, 28.0, 26.6, 24.7. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.85. Found: C, 79.52; H, 7.92.

5-(3,4-Dihydro-2-naphthyl)bicyclo[3.2.0]heptan-6-one (31). Acid **29b** (0.486 g, 1.90 mmol) was converted to the acid chloride **29c** as described above. A solution of **29c** in 2 mL of toluene was added to a solution of triethylamine (2.6 mL, 18.52 mmol) in 20 mL of toluene at reflux under nitrogen. The reaction mixture was heated at reflux for 2 h and worked up as described above to give 0.471 g of crude **31**. Flash chromatography on silica gel (9:1 hexane–EtOAc) gave 0.365 g (81%) of pure **31**: ^{1}H NMR 7.07–7.15 (m, 4), 6.42 (s, 1), 3.26 (dd, 1, J = 18.3, 9.7), 2.97 (m, 1), 2.80 (dd, 2, J = 8.1, 8.1), 2.49 (dd, 1, J = 18.3, 4.3), 2.36 (m, 1), 2.17–2.28 (m, 2), 1.87–1.93 (m, 3), 1.58–1.88 (m, 2); ^{13}C NMR 213.8, 137.8, 134.3, 134.0, 127.0, 126.5, 126.4, 125.8, 121.0, 80.5, 49.2, 35.6, 34.0, 32.9, 27.9, 25.0, 24.6; IR (neat) 2950, 1770, 1740, 1645 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.36; H, 7.38.

5-(3,4-Dihydro-2-naphthyl)bicyclo[3.2.0]heptan-6-ol (32). Sodium borohydride (0.39 g, 10.2 mmol) was added to a solution of ketone **31** (0.243 g, 1.02 mmol) in 25 mL of methanol at room temperature. The reaction mixture was stirred for 1 h, cooled to 0 °C, and quenched with 25 mL of water. The solution was extracted with ether, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.243 g (99%) of **32** as a >19:1 mixture of diastereomers as determined by analysis of the NMR spectrum. The data for the major isomer:

^{1}H NMR 7.00–7.15 (m, 4), 6.19 (s, 1), 4.28 (dd, 1, J = 7.5, 7.5), 2.79 (t, 2, J = 8.1), 2.52 (m, 2), 2.21 (m, 2), 1.5–2.0 (m, 7); ^{13}C NMR 147.6, 134.7, 134.4, 127.1, 126.4, 126.1, 125.5, 118.3, 70.0, 61.2, 35.9, 32.9 (2 C), 31.1, 28.4, 26.1, 25.4; IR ($CHCl_3$) 3615, 2920 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.82; H, 8.32.

Rearrangement of 32. Alcohol **32** (0.128 g, 0.52 mmol) was stirred with KH (0.24 g of 35% dispersion in mineral oil, 2.08 mmol) in 10 mL of THF under N_2 at 0 °C for 2 h. Water was added, and the solution was extracted with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.141 g of crude product containing mineral oil. Flash chromatography of 0.120 g (7:1 hexane–EtOAc) gave 22.0 mg (20%) of **34a**, followed by 83.9 mg (77%) of **34b** that was 90% pure, containing chromatographically inseparable impurities.

The data for **34a**: ^{1}H NMR 7.1–7.4 (m, 4), 4.27 (br s, 1, $w_{1/2} \approx 10$), 3.32 (br s, 1, $w_{1/2} \approx 14$), 2.80 (m, 3), 2.1–2.5 (m, 5), 1.2–1.9 (m, 5) [addition of D_2O simplified the peak at δ 4.27 (ddd, 1, J = 2.9, 6.1, 6.1), decoupling at δ 3.32 removed a coupling from the peak at δ 4.27 (dd, J = 2.9, 6.1)]; ^{13}C NMR 128.5 (CH), 128.4 (CH), 126.6 (CH), 125.9 (CH), 73.3 (CH), 45.2 (CH), 37.4 (CH), 36.3 (CH_2), 34.9 (CH_2), 29.8 (CH_2), 28.3 (CH_2), 27.2 (CH_2), 25.0 (CH_2) (the 4 quaternary carbons were not observed); IR ($CHCl_3$) 3580, 2940 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 213.4 (10 335), 265.1 (2056), 271.8 (2000).

The data for **34b**: ^{1}H NMR 7.0–7.3 (m, 4), 4.47 (ddd, 1, $J \approx$ 4, 4, 4), 3.27 (br s, 1, $w_{1/2} \approx 7$), 2.72 (m, 2), 1.2–2.60 (m, 10), 1.05 (m, 1) [decoupling at δ 3.27 removed a coupling from the peak at δ 4.47 (dd, 1, J = 4, 4)]; ^{13}C NMR 128.2 (CH), 126.1 (CH), 125.8 (CH), 125.0 (CH), 69.4 (CH), 46.6 (CH), 36.1 (CH), 33.9 (CH_2), 33.6 (CH_2), 29.7 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 24.3 (CH_2) (the 4 quaternary carbons were not observed); IR ($CHCl_3$) 3620, 2980 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 220 (10 650), 266 (3520), 270 (3510).

Isomerization of 34b to 35. Treatment of **34b** with 10 equiv of KH at 0 °C for 2 h gave complete conversion to **35**. Alcohol **35** was recrystallized from hexane: mp 118–119 °C; ^{1}H NMR 7.54 (d, 1, J = 7.6), 7.10–7.25 (m, 3), 464 (br s, 1, $w_{1/2}$ = 8), 2.75 (m, 2), 1.4–2.5 (m, 12); ^{13}C NMR 141.1 (C), 135.5 (C), 134.4 (C), 128.0 (C), 127.4 (CH), 126.7 (CH), 126.1 (CH), 122.6 (CH), 64.6 (CH), 45.1 (CH), 35.2 (CH_2), 31.8 (CH_2), 31.6 (CH), 30.7 (CH_2), 28.3 (CH_2), 28.2 (CH_2), 24.2 (CH_2); IR ($CHCl_3$) 3610, 2960 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 219 (18 640), 264 (11 177), 320 (180).

Spiro[cyclohexane-1,1′(2*H*)-3′,4′,5′,6′-tetrahydropentalen]-2′-one (39). Ketone **8** (62.2 mg, 0.33 mmol) was added to neat boron trifluoride etherate (0.5 mL, 4.07 mmol) at 25 °C. The mixture was stirred for 45 min at 25 °C. The reaction was quenched by addition of 2 mL of saturated sodium bicarbonate solution and extracted with two portions of ether. The combined ether layers were washed with brine, dried ($MgSO_4$), and concentrated to give 55.2 mg of crude **39**. Flash chromatography on silica gel (24:1 hexane–EtOAc) gave 47.4 mg (76%) of pure **39**: ^{1}H NMR 2.78 (br s, 2), 2.51 (m, 2), 2.38 (m, 2), 2.14 (m, 2), 1.75 (m, 2), 1.39–1.58 (m, 8); ^{13}C NMR 150.7, 137.9, 40.6, 32.5, 30.9, 30.6, 25.5, 25.1, 22.7 (the carbonyl and quaternary carbons were not observed); IR (neat) 2930, 2850, 1740, 1445 cm^{-1}.

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Registry No. **1a**, 7766-48-5; **1b**, 113404-49-2; **2a**, 38267-20-8; **2b**, 113404-50-5; **3a**, 113404-50-5; **3b**, 113404-52-7; **3c**, 113404-53-8; **3d**, 113404-55-0; **5a**, 104923-37-7; **5b**, 113472-65-4; **5c**, 113472-66-5; **6a**, 113404-57-2; **6b**, 113404-58-3; **6c**, 113404-59-4; **8**, 113404-54-9; **9a**, 113404-60-7; **9b**, 113404-61-8; **9c**, 113404-82-3; (2*Z*,4*E*)-**11**, 113404-56-1; (2*Z*,4*Z*)-**11**, 113404-83-4; **12b**, 113404-62-9; **12c**, 113404-63-0; **14**, 113430-72-1; **15a**, 113404-64-1; **15b**, 97961-71-2; **15c**, 113404-84-5; (2*Z*,4*E*)-**17**, 54716-14-2; (2*Z*,4*Z*)-**17**, 54716-13-1; (2*E*,4*Z*)-**17**, 54716-16-4; (2*E*,4*E*)-**17**, 54716-17-5; **21a**, 113404-69-6; **21b**, 113404-72-1; **21c**, 113404-86-7; **22a**, 113404-73-2; **22b**, 113404-75-4; **22c**, 113404-76-5; **25**, 113404-65-2; **26**, 113404-66-3; **27**, 113404-67-4; **28**, 113404-68-5; **29a**, 113404-77-6; **29b**, 113404-79-8; **29c**, 113404-89-0; **31**, 113404-70-9; **32** (α-isomer), 113404-71-0; **32** (β-isomer), 113472-67-6; **34**, 113404-80-1; **35**, 113404-74-3; **39**, 113404-78-7; methyl crotonate, 18707-60-3; mesyl chloride, 124-63-0; 3-methyl-4-penten-1-ol, 51174-44-8; 3-methyl-4-penten-1-yl mesylate, 113404-81-2; methyl 1-cyclohexeneacetate, 53723-52-7; ethyl (*E*)-2-hexenoate, 27829-72-7; ethyl 3,3-dimethylacrylate, 638-10-8; ethyl (*E*)-3-methyl-2-pentenoate, 24410-84-2; ethyl (*Z*)-3-methyl-2-pentenoate, 27805-84-1; ethyl 3-ethyl-3,8-nonadienoate, 113404-85-6; 3,4-dimethyl-2-(4-pentenyl)-2-cyclobutenone, 113404-87-8; (1-methyl-1-propenyl)bicyclo[3.2.0]heptan-6-one, 113404-88-9; ethyl 3,4-dihydronaphthalene-2-acetate, 63625-94-5.

Total Synthesis and Absolute Configuration of the Antibiotic Oligopeptide (4*S*)-(+)-Anthelvencin A and Its 4*R*-(−) Enantiomer

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The total syntheses of the two enantiomers of anthelvencin A [the naturally occurring isomer (4*S*)-(+)-**1a** and its enantiomer (4*R*)-(−)-**1b**] with enantiomeric excess of 80 ± 4% are described. The absolute configuration of natural anthelvencin A is thereby unambiguously assigned. The two enantiomers, (+)-**1a** and (−)-**1b**, bind to duplex calf thymus DNA with constants of (1.46 ± 0.01) × 10^7 and (1.35 ± 0.01) × 10^7 M^{-1}, respectively, as determined by an ethidium displacement assay.

Anthelvencin A (**1**) is a naturally occurring oligopeptide isolated from the culture of *Streptomyces venezuelae*.[1] It has antibiotic and anthelmintic activity.[1] Anthelvencin A (**1**) is a member of a modest class of oligopeptides, all of which are biologically active. This class of natural products includes kikumycin B (**2**),[2,3] noformycin (**3**),[4] netropsin (**4**),[5] and distamycin A (**5**)[5b,6] (see Scheme I). The biological activities of **4** and **5** arise, in part, from their ability to bind to the minor groove of B-DNA at A·T-rich sequences.[7] The firm and site-specific binding of these sequence-reading oligopeptides and DNA is a net result

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