containing acetone oxime (0.10 g, 1.37 mmol), dichloro derivative **1f** (0.10 g, 0.35 mmol), and $NaHCO_3$ (2.00 g, 23.8 mmol). The reaction mixture rapidly developed a blue color, which faded to colorless during the 48-h stirring period. The reaction mixture was worked-up as described in the general procedure (vide supra). An examination of the crude product by ^1H and ^{13}C NMR indicated that the major components in the mixture were 2-chloro-2-nitropropane and unreacted **1f**, which was recovered in 93% yield.

Acknowledgment. We are grateful for the financial support of the U.S. Army Armament Research Development and Engineering Center, Picatinny Arsenal, NJ (Contract Nos. DAAK10-85-R-0104 and DAAA21-86-C-0101).

Synthesis of the Bicyclo[5.3.1]undecane Moiety (AB Ring System) of Taxanes

Barry B. Snider* and Alban J. Allentoff

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254-9110

Received April 20, 1990

Intramolecular cycloaddition of unsaturated ketenes **15a**, **15b**, and **6** give the 1-vinylbicyclo[3.1.1]heptan-6-ones **16a**, **16b**, and **5** in 51%, 63%, and 30% yield. Addition of vinyllithium to these cyclobutanones at −78 °C gives 1,2-divinylcyclobutane alkoxides that undergo oxy-Cope rearrangements to give (*E*)-bicyclo[5.3.1]undecenones **20a**, **20b**, and **27** in 57%, 63%, and 19% yield. These cyclooctenones contain suitable substituents and functionality for elaboration of the AB ring system of taxane diterpenes. The oxy-Cope rearrangement fails if more highly substituted alkenyllithium reagents are used; so this approach cannot be used for introduction of the C ring of taxane diterpenes.

Introduction

Taxanes, such as taxol, taxinine (**1**), and taxusin are highly oxidized tri- and tetracyclic diterpenes.[1] The compounds are popular synthetic targets,[2] since taxol is a promising antitumor agent.[3] Although numerous synthetic efforts in this direction have been reported,[2] the first synthesis of a natural taxane, taxusin, was only recently reported by Holton.[4] The complex functionality and the tricyclic carbon skeleton make the synthesis of taxanes a challenging synthetic problem.

A major problem in the synthesis of taxanes is the preparation of the eight-membered central B ring. The oxy-Cope rearrangement is an attractive route to medium sized rings that has been applied to taxane synthesis.[5] In particular, oxy-Cope rearrangements of 1,2-divinylcyclobutanols provide an attractive approach to the synthesis of cyclooctenones, as elegantly demonstrated in the synthesis of poitediol by Gadwood.[6f] We have shown that type I intramolecular cycloadditions[7-9] of vinylketenes and alkenes provides an efficient route to 2-vinylcyclobutanones suitable for further elaboration to cyclooctenones by oxy-Cope rearrangements.

A short route to taxinine (**1**) was envisioned based on an intramolecular cycloaddition of trienylketene **6** to give the vinylcyclobutanone **5** (Scheme I). Addition of cyclohexenyllithium reagent **4** to cyclobutanone **5** should give **3**, which might undergo an oxy-Cope rearrangement to give **2**. Dienone **2** contains the complete skeleton and suitable functionality for further elaboration to taxinine. The re-

(1) For a review on isolation and structure of taxanes, see: Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

(2) For leading references to synthetic approaches to taxanes, see: (a) Winkler, J. D.; Lee, C.-S.; Rubo, L.; Muller, C. L. *J. Org. Chem.* **1989**, *54*, 4491. (b) Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277. (c) Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, *28*, 5275. (d) Shea, K. J.; Haffner, C. D. *Tetrahedron Lett.* **1988**, *29*, 1367. (e) Funk, R. L.; Daily, W. J.; Parvez, M. *J. Org. Chem.* **1988**, *53*, 4141. (f) Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1540. (g) Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. (h) Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953.

(3) Denis, J.-N.; Greene, A. E.; Guenard, D.; Guerritte-Voegelin, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917 and references cited therein.

(4) Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

(5) For approaches to taxanes based on oxy-Cope rearrangements, see: (a) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3192. (b) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rodgers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277.

(6) (a) Kahn, M. G. *Tetrahedron Lett.* **1980**, *21*, 4357. (b) Levine, S. G.; MacDaniel, Jr., R. L. *J. Org. Chem.* **1981**, *46*, 2199. (c) Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982**, *47*, 2268. (d) Paquette, L. A.; Andrews, D. R.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 201. Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *J. Org. Chem.* **1983**, *48*, 1149. (e) Lyle, T. A.; Mereyala, H. B.; Pascual, A.; Frei, B. *Helv. Chim. Acta* **1984**, *67*, 774. (f) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 6343; **1984**, *106*, 3869. (g) Miller, S. A.; Gadwood, R. C. *J. Org. Chem.* **1988**, *53*, 2214. (h) Barnier, J. P.; Ollivier, J.; Salaun, J. *Tetrahedron Lett.* **1989**, *30*, 2525. (i) Snider, B. B.; Beal, R. B. *J. Org. Chem.* **1988**, *53*, 4508.

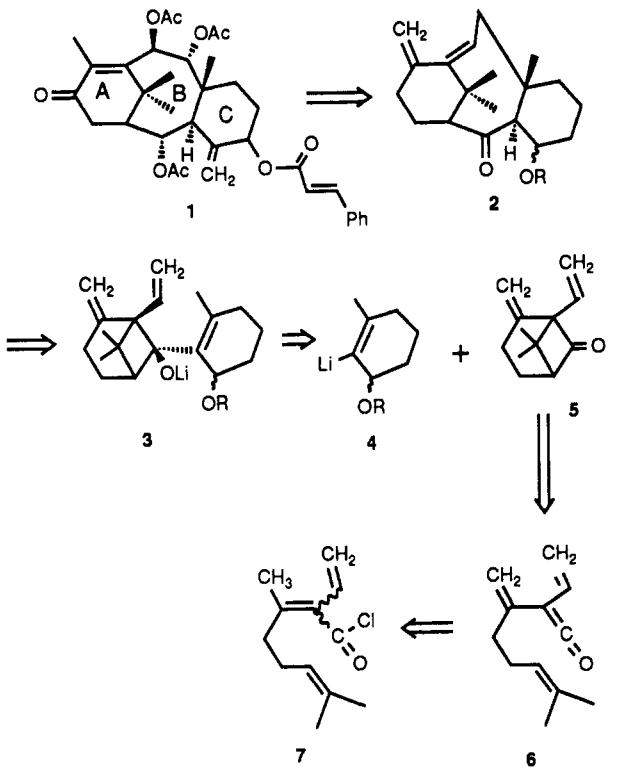
(7) Lee, S. Y.; Kulkarni, Y. S.; Burbaum, B. W.; Johnston, M. I.; Snider, B. B. *J. Org. Chem.* **1988**, *53*, 1848.

(8) For a review, see: Snider, B. B. *Chem. Rev.* **1988**, *88*, 793.

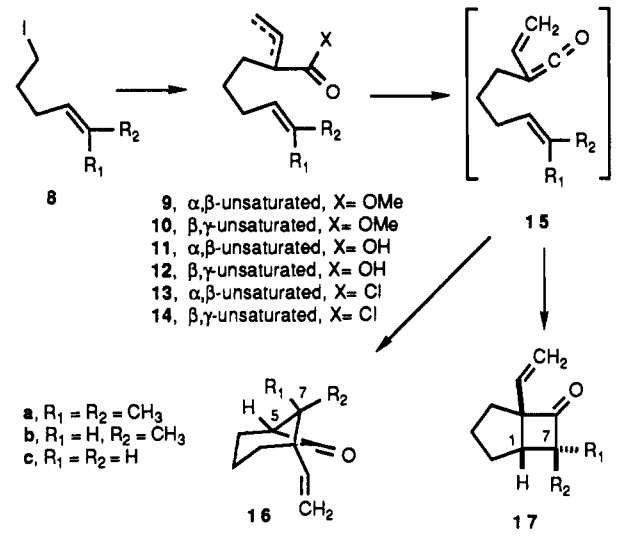
(9) For more recent studies of intramolecular ketene-alkene cycloadditions, see: (a) Veenstra, S. J.; De Mesmaeker, A.; Ernst, B. *Tetrahedron Lett.* **1988**, *29*, 2303. (b) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Syn. Lett.* **1989**, 36. (c) Ghosh, A.; Biswas, S.; Venkateswaran, R. V. *J. Chem. Soc., Chem. Commun.* **1988**, 1421. (d) Sierra, M. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1989**, *111*, 2335. (e) Shishido, K.; Azuma, T.; Shibuya, M. *Tetrahedron Lett.* **1990**, *31*, 219. (f) Ernst, B.; De Mesmaeker, A.; Greuter, H.; Veenstra, S. J. In *Strain and Its Implications in Organic Chemistry*; de Meijere, A., Blechert, S., Eds.; Kluwer: Dordrecht, 1989; pp 207-234. (g) Ghosez, L.; Yong, C. L.; Gobeaux, B.; Houge, C.; Marko, I.; Perry, M.; Saimoto, H. In *Strain and Its Implications in Organic Chemistry*; de Meijere, A., Blechert, S., Eds.; Kluwer: Dordrecht, 1989; pp 235-254. (h) Gobeaux, B.; Ghosez, L. *Heterocycles* **1989**, *28*, 29.

0022-3263/91/1956-0321$02.50/0

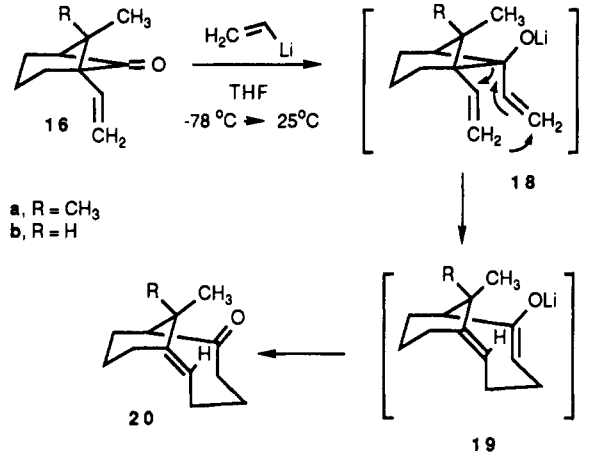
Scheme I



Scheme II



Scheme III



quisite ketene **6** should be readily available from acid chloride **7**.[7]

We began by preparing the model vinylbicyclo[3.1.1]-heptanone **16a** and examining the oxy-Cope rearrangements of divinylcyclobutanols obtained from it. We anticipated that **16a** would be readily available from acid chloride **13a** (Scheme II). We have previously shown that treatment of acid chloride **13c** with triethylamine in toluene at reflux gives ketene **15c**, which undergoes an intramolecular cycloaddition to give bicyclo[3.2.0]heptanone **17c**.[7] We expected that introduction of two methyl groups onto the end of the double bond would change the regiochemistry of the cycloaddition, giving the desired bicyclo[3.1.1]heptanone **16a**.

Results and Discussion

Reaction of methyl crotonate with LDA in THF containing 1 equiv of HMPA at −78 °C affords the dienolate,[7,10] which is treated with iodide **8a** to give 65% of a 6:4 mixture of esters **9a** and **10a**. Hydrolysis with aqueous lithium hydroxide gives 79% of a 4:1 mixture of acids **11a** and **12a**. The mixture of acids is converted to the acid chlorides **13a** and **14a** by treatment with oxalyl chloride and sodium hydride in benzene at 25 °C. Addition of the crude acid chloride mixture to Et_3N in toluene at reflux gives ketene **15a**, which undergoes regiospecific cycloaddition as expected to give **16a** in 51% yield from **11a** and **12a**.

We studied the intramolecular cycloaddition of vinylketene **15b** to determine the regiochemistry of the cycloaddition with a trans-1,2-disubstituted alkene. Alkylation of methyl crotonate with iodide **8b** give 70% of ester **9b**. Hydrolysis with aqueous lithium hydroxide provides 84% of acid **11b**, which is converted to acid chloride **13b**. Addition of a solution of acid chloride **13b** to Et_3N in toluene at reflux affords ketene **15b**, which undergoes cycloaddition to give 63% of **16b** and 13% of **17b** from **11b**.

The structures and stereochemistry of **16a**, **16b**, and **17b** follow from an analysis of the ^1H NMR spectra. The coupling constant $J_{5,7}$ in **16b** is 1 Hz, a value consistent only with a 7-*anti*-methylbicyclo[3.1.1]heptan-6-one with a calculated dihedral angle of 104°.[11] The coupling constant $J_{1,7}$ in **17b** is 4.4 Hz, a value consistent only with a 7-*exo*-methylbicyclo[3.2.0]heptan-6-one.[12]

The total yield of cycloadducts in the cycloaddition of **15b**, 76%, is considerably higher than that from **15a**, 51%. This is due to steric hindrance, since we have previously shown that alkyl substituents cis to the tether (R_1) on the alkene hinder the adoption of a $_\pi2_s + _\pi2_a$ transition state.[13] The bridged isomer **16b** is the major product from **15b** as expected, since leading bond formation between the ketene carbonyl carbon should occur with the internal alkene carbon forming an entropically favored six-membered ring transition state.

Model studies for the oxy-Cope rearrangement of **3** were carried out with 1-vinylbicyclo[3.1.1]heptan-6-ones **16a** and **16b**. Addition of a solution of **16a** to vinyllithium in THF

(10) (a) Krebs, E.-P. *Helv. Chim. Acta* **1981**, *64*, 1023. (b) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163. (c) Ikeda, Y.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5181. (d) Alcock, S. G.; Baldwin, J. E.; Bohlmann, R.; Harwood, L. M.; Seeman, J. I. *J. Org. Chem.* **1985**, *50*, 3526. (e) Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1971**, *36*, 3290.

(11) MMX from Serena Software, 489 Serena Lane, Bloomington, IN 47401, was used for calculations of heats of formation. MODEL version KS 2.94, obtained from Prof. Steliou, University of Montreal, was used for structure input, MM2 calculations, and conformational searching.

(12) Rey, M.; Roberts, S. M.; Dreiding, A. S.; Roussel, A.; Vanlierde, H.; Toppet, S.; Ghosez, L. *Helv. Chim. Acta* **1982**, *65*, 703.

(13) Snider, B. B.; Walner, M. *Tetrahedron* **1989**, *45*, 3171.

at −78 °C, stirring for 1 h, and warming to 25 °C affords bicyclo[5.3.1]undecenone **20a** in 57% yield (Scheme III). A similar reaction with **16b** provides 63% of **20b**. Addition of vinyllithium occurs exclusively from the less hindered face to give divinyl alkoxide **18**. Oxy-Cope rearrangement occurs through a chair-like transition state to give enolate **19**; protonation gives **20** with an (*E*)-cyclooctene.

The structure of **20** follows from analysis of the coupling constants to the alkenyl hydrogen and from NOE studies. The alkenyl hydrogen is coupled to the adjacent methylene group with coupling constants of 4 and 11 Hz. These couplings are much larger than those observed in (*Z*)-cyclooctenes but entirely consistent with those observed in related (*E*)-cyclooctenes[6e] and expected on the basis of calculated dihedral angles of 51° and 174°.[11] In **20a**, there is a large NOE enhancement (10%) of the alkenyl hydrogen at δ 5.05 on irradiation of the upfield methyl group at δ 1.20. This NOE enhancement is expected for **20a** in which the methyl carbon and alkenyl hydrogen are calculated to be separated by only 2.50 Å.[11] In the *Z* isomer, the separation between the methyl carbon and alkenyl hydrogen is calculated to be 4.24 Å.

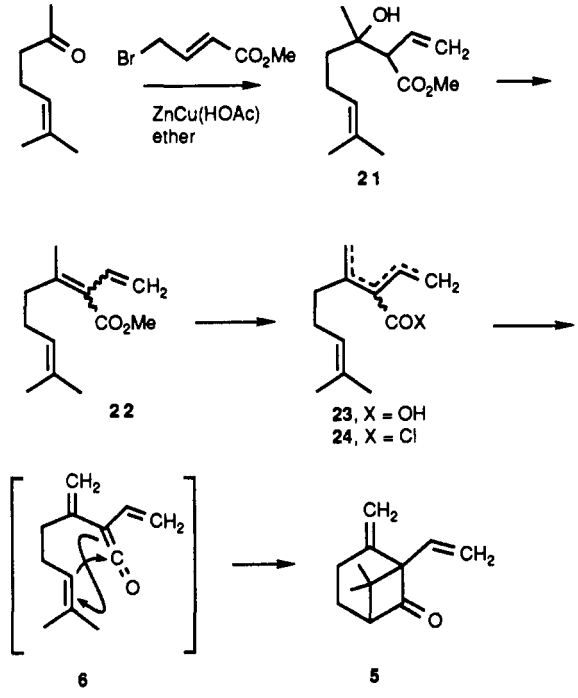
Most examples of oxy-Cope rearrangements of 1,2-divinylcyclobutanols are in molecules in which the alkene substituents are cis on the cyclobutane ring, permitting rearrangement to occur through either a boat or a chair transition state.[6] *trans*-1,2-Divinylcyclobutanols must undergo the oxy-Cope rearrangement either through a chair-like transition state to give an (*E*)-cyclooctene or through a stepwise process. The formation of (*E*)-cyclooctenes in oxy-Cope rearrangments of *trans*-divinylcyclobutanols has been observed by Gadwood[6f] and Frei.[6e]

The driving force for the oxy-Cope rearrangement is relief of cyclobutane ring strain. Even though **20** is calculated to be 8 kcal/mol more strained than the corresponding *Z* isomer, it is calculated to be more stable than the divinylcyclobutanol obtained by protonation of alkoxide **18** by 18 kcal/mol.[11] Molecular mechanics calculations[11] indicate that the conformation of **20** shown, which would be formed directly in the oxy-Cope rearrangement, is the most stable by 4 kcal/mol. This contrasts with a recent example reported by Paquette in which an oxy-Cope rearrangement gave an isolable high energy atropisomer.[5b]

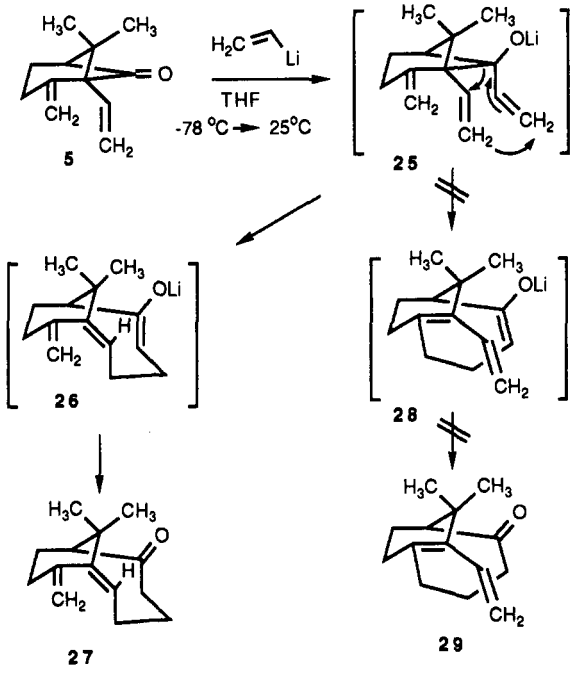
Having successfully demonstrated that **18** undergoes oxy-Cope rearrangement, we turned our attention to the preparation of the desired vinylcyclobutanone **5**. Reformatsky reaction of methyl 4-bromocrotonate with 6-methyl-5-hepten-2-one in the presence of zinc–copper couple with traces of acetic acid in ether at reflux, as developed by Hudlicky[14] to achieve selective attack from the α carbon, furnishes **21** as a mixture of diastereomers (Scheme IV). The alcohol was acetylated with acetic anhydride and DMAP and the resulting acetate treated with DBU in dry DME to give 53% of **22** as a 3:2 mixture of stereoisomers. Hydrolysis with aqueous lithium hydroxide affords 74% of a complex mixture of acids **23**. This mixture was converted to the acid chloride mixture **24** by treatment with oxalyl chloride and sodium hydride in benzene. Dropwise addition of the acid chloride mixture to a solution of Et_3N in benzene at reflux provides 30% of desired vinylcyclobutanone **5**. At higher temperatures, in toluene at reflux, the yield of **5** is lower and monocyclic ketones are formed.

Addition of vinyllithium to vinylcyclobutanone **5** will give triene alkoxide **25**, which could undergo two different oxy-Cope rearrangements to give either the desired bicyclo[5.3.1]undecenone **27** or the undesired cyclooctene **29** (Scheme V). We were confident that the exo methylene group would not interfere with the desired oxy-Cope rearrangement leading to **27**, since we have shown that the diene lacking the 1-vinyl group of **25** does not undergo oxy-Cope rearrangement.[6i] Addition of vinylcyclobutane **5** to vinyllithium in THF at −78 °C followed by careful quenching with water at −78 °C affords 19% of the desired bicyclo[5.3.1]undecenone **27** as the only characterizable product. The structure of **27** was established analogously to that of **20**. The alkenyl hydrogen absorbs as a doublet of doublets, J = 12.1 and 4.2 Hz, and there is an 18% NOE enhancement of the alkenyl hydrogen at δ 5.12 on irradiation of the methyl group at δ 1.20. The formation of bicyclo[5.3.1]undecenone **27** indicates that the triene alkoxide **25** undergoes the desired rearrangement, although

Scheme IV

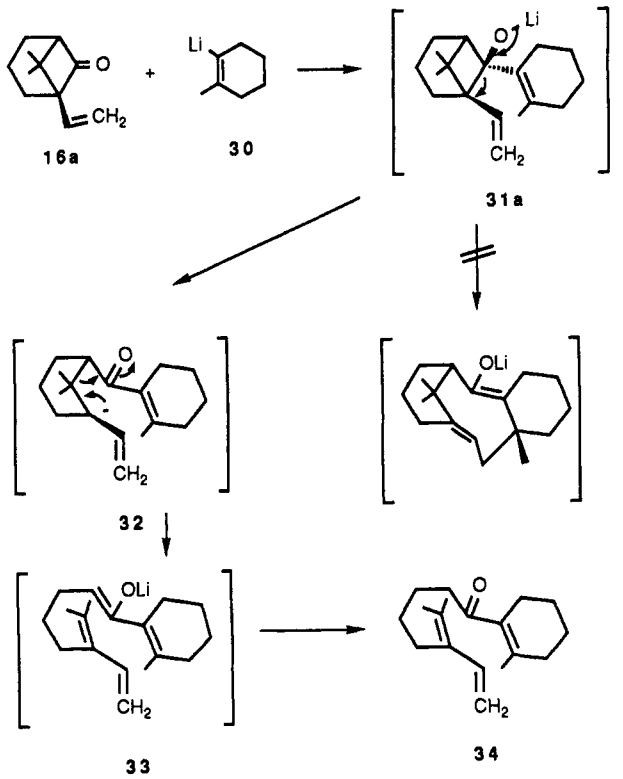


Scheme V



(14) Rice, L. E.; Boston, M. C.; Finklea, H. O.; Suder, B. J.; Frazier, J. O.; Hudlicky, T. *J. Org. Chem.* **1984**, *49*, 1845.

Scheme VI



in considerably lower yields than the diene alkoxide **18**.

Having demonstrated that vinylcyclobutanone **5** can be easily prepared and that triene alkoxide **25** undergoes the desired oxy-Cope rearrangement, we turned our attention to the addition of more highly substituted alkenyllithium reagents to bicycloheptanone **16a**. Treatment of 1-iodo-2-methylcyclohexene[15] with 2 equiv of *tert*-butyllithium in THF at −78 °C gives the desired lithium reagent **30**.[16] Slow addition of ketone **16a** to a solution of **30** followed by warming the solution to 25 °C provides none of the desired oxy-Cope product. The only characterizable product is 43% of trienone **34**. Fragmentation of **31a** gives **32**, which fragments further to give enolate **33**; protonation gives **34** (Scheme VI).

Addition of bicycloheptanone **16a** to lithium reagent **30** at −78 °C followed by quenching with acetic acid at −78 °C gives 70% of **31b**. Thermolysis of **31b** for 37 h at 85 °C in benzene-d_6 results in clean retro-ene reaction, giving 75% of **39**. *trans*-1,2-Divinylcyclobutanols have been previously shown to undergo facile retro-ene reactions.[6h] We attempted to prevent the retro-ene reaction by protecting the hydroxyl group as a silyl ether. Unfortunately, the hydroxyl group in alcohol **31b** is too sterically hindered and could not be silylated. Reaction of **31b** with potassium hydride in THF at 0 °C gives a complex mixture containing 17% of **39** (Scheme VII).

These results indicated that the substituents on the alkenyllithium **30** are not preventing addition of the lithium reagent to the ketone but are preventing oxy-Cope rearrangement.[17] Examination of the conformation necessary for a chair-like transition state in the oxy-Cope rearrangement provides a possible explanation for this observation. The minimum energy conformations A of **18** and **31a** are calculated to have dihedral angles between the oxygen and the alkenyl carbon of 70–80°. Oxy-Cope rearrangement through a chair-like transition state requires a dihedral angle of approximately 0° as shown in B. For **18**, in which R_1 and R_3 are hydrogen, the reactive conformation B is calculated to be less stable than A by 5 kcal/mol. For **31a**, in which R_1 is an alkyl chain and R_3 is a methyl group, the reactive conformation B is calculated to be less stable than A by 22 kcal/mol due to the steric interactions shown. Therefore **31a** cannot adopt the required conformation for an oxy-Cope rearrangement and undergoes only fragmentation reactions.

If this analysis is correct, introduction of a substituent at R_2 should not prevent any oxy-Cope rearrangement. Addition of **16a** to (*E*)-1-butenyllithium[16] in THF at −78 °C, stirring for 30 min, and slow warming of the solution to 25 °C gives 30% of **46** as a single stereoisomer, whose stereochemistry is tentatively assigned as shown, since it would be expected from an oxy-Cope rearrangement of **45** proceeding through a chair-like transition state (Scheme VIII). The structure of **46** was established analogously to that of **20**. The alkenyl hydrogen absorbs as a doublet of doublets, J = 11.5 and 3.7 Hz, and there is a 21% NOE enhancement of the alkenyl hydrogen at δ 5.08 on irradiation of the methyl group at δ 1.19.

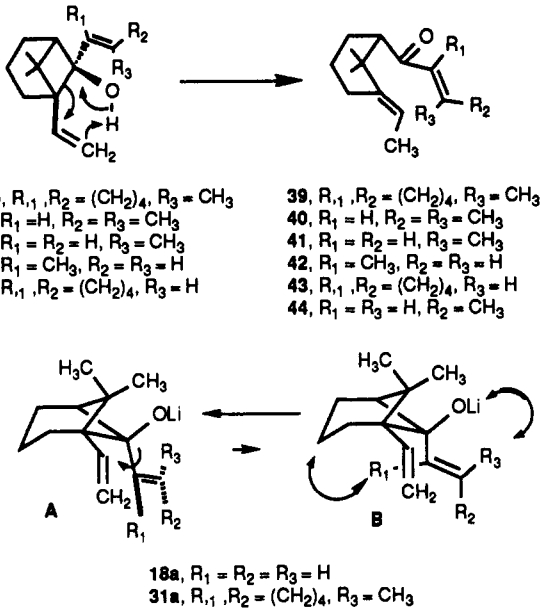
We have now established that the oxy-Cope rearrangement can occur if R_2 is an alkyl group and that it cannot occur if both R_1 and R_3 are alkyl groups. We examined the addition of (2-methyl-1-propenyl)lithium, *cis*-1-propenyllithium, (1-methylethenyl)lithium, and 1-cyclohexenyllithium to **16a** to determine whether oxy-Cope rearrangement would occur if only one of R_1 and R_3 is an alkyl group. Calculations suggested that the reactive conformer B of **36** is less stable than the minimum energy conformer A by only 10 kcal/mol due to interaction of methyl group at R_3 with the oxygen and that the reactive conformer of B of **37** is less stable than the miminum energy conformer by 16 kcal/mol due to the interaction of methyl group at R_1 with the cyclohexane methylene group.

The desired alcohols **35** (68%), **36** (56%), **37** (71%), and **38** (53%) are obtained by addition of **16a** to the appropriate alkenyllithium reagent[16] at −78 °C followed by quenching with acetic acid at −78 °C. Fragmentation occurs on warming the lithium alkoxide precursors to **35** and **36** to 25 °C or on treatment of the alcohols with potassium hydride at 25 °C in THF. The lithium alkoxide precursors to **37** and **38** are stable at 25 °C. Thermolysis of the alcohols **35**, **37**, and **38** results in clean retro-ene reaction to give **40** (91%, 72 °C, 140 h), **42** (77%, 90 °C, 156 h), and **43** (70%, 90 °C, 119 h). Thermolysis of **36** in benzene for 186 h at 72 °C provides a mixture of the retro-ene product **41** and the *E* isomer **44**. Further heating at 105 °C for 360 h completes isomerization of the double bond, affording 77% of the *E* isomer **44**.

Oxy-Cope rearrangement of *cis*-1-alkynyl-2-vinylcyclobutanols has been developed by Gadwood as a route to cyclooctadienones.[6f,g] We examined the addition of 1-pentynyllithium to **16a** in an attempt to prepare a bicyclo[5.3.1]undecadienone containing an α,β-unsaturated enone that would permit the elaboration of the taxane C ring. Addition of 1-pentynyllithium to **16a** at −78 °C followed by slow warming to 25 °C and quenching affords alcohol **47**. Treatment of alcohol **47** with potassium hydride in THF at 25 °C gives a complex mixture. Thermolysis of alcohol **47** for 21 h at 100 °C provides only the retro-ene adduct **48**. Apparently, the trans arrangement of the alkenyl and alkynyl side chains on the cyclobutane

(15) Martinez, G.; Alvarez, R. M.; Fraile, A. G.; Subramanian, L. R.; Hanack, M. *Synthesis* **1989**, 222.
(16) (a) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847. (b) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785.
(17) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107.

Scheme VII



31b, R_1,R_2 = $(CH_2)_4$, R_3 = CH_3
35, R_1 =H, R_2 = R_3 = CH_3
36, R_1 = R_2 = H, R_3 = CH_3
37, R_1 = CH_3, R_2 = R_3 = H
38, R_1 ,R_2 = $(CH_2)_4$, R_3 = H

39, R_1 ,R_2 = $(CH_2)_4$, R_3 = CH_3
40, R_1 = H, R_2 = R_3 = CH_3
41, R_1 = R_2 = H, R_3 = CH_3
42, R_1 = CH_3, R_2 = R_3 = H
43, R_1 ,R_2 = $(CH_2)_4$, R_3 = H
44, R_1 = R_3 = H, R_2 = CH_3

18a, R_1 = R_2 = R_3 = H
31a, R_1 ,R_2 = $(CH_2)_4$, R_3 = CH_3

precludes oxy-Cope rearrangement.

We have established that the desired 1-vinylbicyclo-[3.1.1]heptan-6-ones **16** and **5** can be easily prepared by short and efficient routes. The oxy-Cope rearrangement of divinylcyclobutane alkoxides **18** and **25**, obtained by addition of vinyllithium to **16** and **5**, are successful, giving **20** and **27**. The oxy-Cope rearrangement fails with more hindered alkenyllithium reagents needed for the elaboration of the taxane C ring.

Experimental Section

Benzene, diisopropylamine, toluene, and triethylamine were dried by distillation from calcium hydride. Diethyl ether and THF were dried by distillation from sodium benzophenone ketyl. All air- and moisture-sensitive reactions were run under an inert atmosphere in flame-dried glassware with magnetic stirring. Reagents were added via oven-dried syringes through rubber septa. 6-Iodo-2-methyl-2-hexene (**8a**) was prepared by an orthoester Claisen rearrangement of 2-methyl-3-buten-2-ol with triethyl orthoacetate[18] and reduction of the ester with lithium aluminum hydride.[19] The alcohol was converted to the mesylate with mesyl chloride in CH_2Cl_2, which was reacted with sodium iodide in acetone. (*E*)-6-Iodo-2-hexene (**8b**) was prepared in the same manner from the commercially available alcohol.

Methyl (*E*)-2-Ethylidene-7-methyloct-6-enoate (9a) and Methyl 2-Ethenyl-7-methyloct-6-enoate (10a). *n*-Butyllithium (5.15 mL of a 2.6 M solution in hexane, 13.4 mmol) was added to a solution of diisopropylamine (1.36 g, 13.4 mmol) in THF at 0 °C. The solution was cooled to −78 °C and was treated with HMPA (2.65 g, 14.8 mmol) and then methyl crotonate (1.22 g, 12.2 mmol) as previously described.[10] 2-Methyl-6-iodohex-2-ene (**8a**) (3.60 g, 15.9 mmol) was added at −78 °C, and the resulting solution was stirred at −78 °C for 1 h and then at 0 °C for 4 h. The reaction was quenched with water and was worked up to give 3.15 g of crude product. Purification of a 3.11-g sample of the crude product by flash chromatography on silica gel (96:4 hexane/EtOAc) gave 1.53 g (65%) of pure **9a** and **10a** as an inseparable 6:4 mixture: IR (neat) 2923, 2858, 1742, 1716, 1648, 1433, 1375, 1273, 1258, 1192, 1154, 1123, 1068, 916, 746 cm^{-1}; ^1H NMR **9a** 6.84 (q, 1, J = 7.2), 5.06–5.15 (m, 1), 3.72 (s, 3), 2.30 (br t, 2, J = 7.4), 1.92–2.06 (m, 2), 1.79 (d, 3, J = 7.2), 1.69 (br s, 3), 1.60 (br s, 3), 1.43 (m, 2); **10a** 5.81 (ddd, 1, J = 8.7, 11.0, 17.4), 5.06–5.15 (m, 3), 3.68 (s, 3), 3.02 (dt, 1, J = 7.5, 7.5), 1.22–1.78 (m, 6), 1.69 (br s, 3), 1.60 (br s, 3).

(*E*)-2-Ethylidene-7-methyloct-6-enoic Acid (11a) and 2-Ethenyl-7-methyloct-6-enoic Acid (12a). Esters **9a** and **10a** (0.920 g, 4.68 mmol) were added to a mixture of water (24 mL), DME (58 mL), and lithium hydroxide[20] (1.12 g, 46.8 mmol), and the resulting mixture was stirred at 25 °C for 60 h. Normal workup gave 0.832 g of crude acids. Purification of a 0.813-g portion by flash chromatography on silica gel (75:25:0.2 hexane/EtOAc/AcOH) gave 0.791 g (79%) of pure **11a** and **12a** as an inseparable 4:1 mixture: IR (neat) 2923, 1688, 1643, 1417, 1289, 1270, 924, 748 cm^{-1}; ^1H NMR **11a** 7.05 (q, 1, J = 7.1), 5.12–5.28 (m, 1), 2.30 (br t, 2, J = 7.4), 2.00 (br dt, 2, J = 7, 7), 1.82 (d, 3, J = 7.1), 1.69 (s, 3), 1.60 (s, 3), 1.46 (m, 2); ^{13}C NMR **11a** 173.6, 140.1, 132.8, 131.7, 124.3, 29.0, 27.9, 25.7 (2 carbons), 17.7, 14.4; ^1H NMR **12a** 5.83 (ddd, 1, J = 8.7, 11.0, 17.4), 5.12–5.28 (m, 3), 3.04 (dt, 1, J = 7.5, 7.5), 1.51–1.90 (m, 6), 1.69 (s, 3), 1.60 (s, 3); ^{13}C NMR **12a** 180.9, 135.6, 131.8, 124.0, 117.5, 50.1, 31.6, 27.6, 27.2, 25.7, 14.4. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.30; H, 10.03.

1-Ethenyl-7,7-dimethylbicyclo[3.1.1]heptan-6-one (16a). A mixture of acids **11a** and **12a** (0.721 g, 3.96 mmol) and NaH (0.475 g, 60% dispersion, washed twice with hexanes, 11.9 mmol) in benzene (21 mL) was treated with oxalyl chloride (2.51 g, 19.8 mmol) and stirred at 25 °C for 1 h. Excess oxalyl chloride and solvent were removed in vacuo to give acid chlorides **13a** and **14a**, which were added to Et_3N (6.07 g, 31.7 mmol) in 75 mL of toluene at reflux. The solution was heated at reflux for 5 h and worked up to give 1.19 g of crude product. Purification of a 1.15-g portion by flash chromatography on silica gel (97:3 hexane/EtOAc) gave 0.321 g (53%) of pure **16a**: ^1H NMR 5.73 (dd, 1, J = 11.0, 17.8), 5.20 (dd, 1, J = 17.8, 1.7), 5.15 (dd, 1, J = 11.0, 1.7), 2.54 (dd, 1, H_5, J = 5.2, 1.7), 2.35 (ddd, 1, J = 10.7, 13.0, 8.2), 1.90–2.24 (m, 2), 1.50–1.88 (m, 3), 1.16 (s, 3), 1.05 (s, 3); ^{13}C NMR 214.5 (C=O), 133.8 (HC=), 116.3 (H_2C=), 68.4 (C_1), 63.1 (C_5), 34.1 (C_7), 33.4 (CH_2), 27.8 (CH_2), 25.8 (CH_3), 16.8 (CH_2), 15.8 (CH_3); IR (neat) 2925, 2868, 1770, 1634, 1449, 1368, 991, 920 cm^{-1}; exact mass calcd for $C_{11}H_{16}O$ 164.1201, found 164.1198.

Methyl (*E*)-2-Ethylidene-6(*E*)-octenoate (9b). Methyl crotonate (1.09 g, 10.9 mmol) was converted to the dienolate at −78 °C as described above and treated with (*E*)-6-iodo-2-hexene (**8b**) (2.98 g, 14.2 mmol) in 3 mL of THF at −78 °C. The solution was stirred at −78 °C for 1 h and then at 0 °C for 3 h and worked up to give 2.84 g of crude product. Purification of a 2.79-g portion by flash chromatography on silica gel (92:8 hexane/EtOAc) gave 1.36 g (70%) of pure **9b**: ^1H NMR 6.85 (br q, 1, J = 7.1), 5.24–5.60 (m, 2), 3.72 (s, 3), 2.30 (dd, 2, J = 7.8, 7), 2.00 (m, 2), 1.79 (d, 3, J = 7.1), 1.65 (br s, 3), 1.44 (ddt, 2, J = 7, 7.8, 5.0); IR (neat) 2940, 2864, 1720, 1656, 1440, 1385, 1261, 1195, 1175, 1140, 968 cm^{-1}.

(*E*)-2-Ethylidene-6(*E*)-octenoic Acid (11b). Hydrolysis of crude ester **9b** as described above gave 0.792 g of crude **11b**. Purification of a 0.765-g portion by flash chromatography on silica gel (75:25:0.2 hexane/EtOAc/AcOH) gave 0.697 g (84%) of pure **11b** as a clear oil: ^1H NMR 7.01 (q, 1, J = 7.3), 5.41–5.45 (m, 2), 2.29 (dd, 2, J = 7.4, 7.7), 1.97–2.03 (m, 2), 1.83 (d, J = 7.3), 1.64 (ddt, 3, J = 3.4, 1.3, 1.3), 1.44 (ddt, 2, J = 7.4, 7.7, 5.0); ^{13}C NMR 173.5, 140.2, 132.7, 131.0, 125.1, 32.4, 28.7, 25.6, 17.9, 14.4; IR (neat) 2940, 1690, 1645, 1420, 1290, 1183, 750 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.40; H, 9.65.

***anti*-1-Ethenyl-7-methylbicyclo[3.1.1]heptan-6-one (16b) and *exo*-5-Ethenyl-7-methylbicyclo[3.2.0]heptan-6-one (17b).** A solution of acid **11b** (0.585 g, 3.48 mmol) in 19 mL of benzene was treated with oxalyl chloride (2.21 g, 17.4 mmol) at 0 °C under nitrogen. The mixture was stirred at 25 °C for 1 h and was then warmed to 70 °C for 30 min. The solution was cooled and the solvent was removed in vacuo to give acid chloride **13b**. The acid chloride was dissolved in 15 mL of dry toluene and the resulting solution was added dropwise over 20 min to a solution of triethylamine (2.82 g, 27.8 mmol) in 66 mL of dry toluene at reflux. The solution was heated at reflux for an additional 5 h, cooled, and worked up to give 0.993 g of crude product. Purification of a 0.950-g portion by flash chromatography on silica gel (97:3

(18) Trust, R. I.; Ireland, R. E. *Organic Synthesis*; Wiley: New York, 1988; Collect. Vol. 6, p 606.
(19) Nystrom, R. F.; Brown W. G. *J. Am. Chem. Soc.* **1947**, *69*, 2548.
(20) Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433.

pentane/ether) gave an initial fraction containing 64.2 mg (13%) of **17b** followed closely by a fraction containing 0.317 g (63%) of pure **16b**.

Data for **16b**: ^{1}H NMR 5.74 (dd, 1, J = 11.0, 17.8), 5.28 (dd, 1, J = 17.8, 1.7), 5.20 (dd, 1, J = 11.0, 1.7), 2.66 (ddd, 1, H_5, J = 1, 3.4, 3.5), 2.22–2.39 (m, 4), 2.07 (dq, 1, H_7, J = 1.0, 6.9), 1.79–1.88 (m, 1), 1.65 (m, 1), 1.02 (d, 3, J = 6.9); ^{13}C NMR 212.8 (C=O), 133.7 (HC=), 116.8 (H_2C=), 68.8 (C_1), 62.0 (C_5), 39.0 (CH_2), 36.8 (C_7), 33.0 (CH_2), 18.1 (CH_2), 15.5 (CH_3); IR (neat) 2942, 2862, 1770, 1632, 1452, 1414, 1381, 1264, 1060, 991, 922 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.04; H, 9.41.

Data for **17b**: ^{1}H NMR 5.96 (dd, 1, J = 10.6, 17.4), 5.17 (dd, 1, J = 1.2, 17.4), 5.05 (dd, 1, J = 1.2, 10.6), 2.63 (dq, 1, H_7, J = 4.4, 7.6), 2.35–2.39 (m, 1), 2.14 (br dd, 1, J = 5.8, 12.6), 1.46–1.98 (m, 5), 1.21 (d, 3, J = 7.6); ^{13}C NMR 217.8 (C=O), 137.4 (HC=), 114.3 (H_2C=), 76.0 (C_5), 56.7 (CH), 45.0 (CH), 36.5 (CH_2), 33.1 (CH_2), 26.1 (CH_2), 14.8 (CH_3); IR (neat) 2953, 2868, 1775, 1637, 1456, 917, 731 cm^{-1}.

11,11-Dimethyl-(6*E*)-bicyclo[5.3.1]undec-6-en-2-one (20a). A solution of ketone **20a** (34.5 mg, 0.210 mmol) in THF was added by syringe over 4 min to a solution of vinyllithium (0.190 mL of a 1.65 M solution in THF, 0.315 mmol) in THF at −78 °C. During addition, the tip of the syringe needle was held below the surface of the solution to chill the ketone before it reacts with the vinyllithium.[6c,i] The resulting solution was stirred for 1 h at −78 °C, allowed to warm to 25 °C over 3 h, and stirred at 25 °C for 1 h. The reaction was quenched with saturated bicarbonate solution and was worked up to give 50.1 mg of crude **20a**. Purification of a 41.9-mg portion by flash chromatography on silica gel (95:5 hexane/EtOAc) gave 19.3 mg (57%) of pure **20a**: ^{1}H NMR 5.05 (br ddd, 1, H_6, J = 4.5, 11.1, 1.8), 2.68 (dd, 1, J = 9.8, 14.7), 1.72–2.59 (m, 12), 1.25 (s, 3), 1.20 (s, 3); ^{13}C NMR 215.6 (C=O), 147.0 (C=), 121.4 (HC=), 67.4 (CH), 45.9 (C), 39.6 (CH_2), 31.9 (CH_2), 28.9 (CH_2), 24.4 (CH_2), 23.8 (CH_3), 23.4 (CH_3), 20.89 (CH_2), 20.86 (CH_2); IR (neat) 2930, 1682, 1479, 1462, 1442, 1385, 1322, 1287, 1197, 1172, 1115, 1089, 1032, 916, 864, 838, 727 cm^{-1}; exact mass calcd for $C_{13}H_{20}O$ 192.1514, found 192.1514.

***anti*-11-Methyl-(6*E*)-bicyclo[5.3.1]undec-6-en-2-one (20b).** To a solution of vinyllithium (0.58 mL of a 1.65 M solution in THF, 0.965 mmol) in 6.2 mL of THF at −78 °C was added cyclobutanone **16b** (96.6 mg, 0.643 mmol) in 1 mL of THF. The solution was stirred at −78 °C for 1.5 h, allowed to warm to 25 °C over 3 h, stirred at 25 °C for 1 h, and worked up to give 0.148 g of crude **20b**. Purification of a 0.138-g portion by flash chromatography on silica gel (95:5 hexane/EtOAc) gave 66.7 mg (63%) of pure **20b**: ^{1}H NMR 4.94 (br dd, 1, J = 3.9, 11.8), 2.73–2.88 (m, 1), 2.60–2.66 (m, 2), 2.50–2.58 (m, 1), 1.74–2.41 (m, 10), 1.16 (d, 3, J = 6.9); ^{13}C NMR 216.3 (C=O), 145.4 (C=), 119.9 (=CH), 63.0 (CH), 47.8 (CH), 39.3 (CH_2), 31.5 (CH_2), 29.9 (CH_2), 28.3 (CH_2), 26.0 (CH_2), 22.5 (CH_2), 13.7 (CH_3); IR (neat) 2929, 1680, 1450, 1370, 1323, 1290, 1180, 1130, 1098, 1080, 1020, 923, 908, 870, 835 cm^{-1}; exact mass calcd for $C_{12}H_{18}O$ 178.1358, found 178.1362.

Methyl 3,7-dimethyl-2-ethenyl-3-hydroxyoct-6-enoate (21) was prepared by the procedure of Hudlicky.[14] A flame-dried flask under nitrogen atmosphere, equipped with an addition funnel and condenser, was charged with cupric acetate monohydrate (0.358 g, 1.79 mmol) followed by 10 mL of acetic acid, and the resulting solution was heated to 80 °C. To the stirred hot solution was added zinc powder (6.27 g, 96.0 mmol) in one part and the resulting brown suspension was stirred at 80 °C for 3 min and was allowed to cool to 25 °C. The mixture was then washed (via syringe) with four 20-mL portions of dry ether to remove excess acetic acid. Ether (50 mL) was then added followed by a few crystals of iodine. A solution of 6-methylhept-5-en-2-one (3.03 g, 24.0 mmol) and methyl-4-bromocrotonate (4.78 g, 24 mmol) in 20 mL of ether was placed in the addition funnel, and a few drops of this solution were added to the solution. After several minutes the iodine color in the reaction mixture disappeared and the solution became warm. The solution was then heated to reflux and the solution of ketone and methyl 4-bromocrotonate was added dropwise over 45 min. After addition was complete the solution was heated at reflux for an additional 3 h and was then cooled. The mixture was then washed with saturated ammonium chloride solution and the aqueous layer was extracted twice with ether. The combined organic layers were dried and solvent was removed to give 7.58 g of crude **21** as a mixture of diastereomers, which was used without further purification: ^{1}H NMR 5.89–6.04 (m, 1), 5.26 (br dd, 1, J = 10.2, 1.7), 5.22 (br dd, 1, J = 17.4, 1.7), 5.08 (br t, J = 7.2), 3.73 (s, 3), 3.12 (d, 1 × 0.6, J = 9.5), 3.11 (d, 1 × 0.4, J = 9.5), 1.94–2.15 (m, 2), 1.68 (br s, 3), 1.61 (br s, 3), 1.38–1.58 (m, 2), 1.22 (s, 3 × 0.4), 1.16 (s, 3 × 0.6); IR (neat) 3516, 2948, 1726, 1438, 1201, 1169, 916, 733 cm^{-1}.

Methyl (*E*)- and (*Z*)-3,7-Dimethyl-2-ethenyl-2,7-octadienoate (22). Crude hydroxy ester **21** (7.51 g) was stirred with Et_3N (2.41 g, 23.8 mmol) and 4-(dimethylamino)pyridine (0.291 g, 2.38 mmol) in 50 mL of acetic anhydride for 24 h at 25 °C. The solution was taken up in ether and 10% hydrochloric acid, and the layers were separated. The organic layer was washed with saturated aqueous bicarbonate solution and was dried. Removal of the solvent gave 7.93 g of the crude acetates, which were used for the next step.

The acetates were added to a solution of DBU (5.39 g, 35.4 mmol) in 30 mL of dry DME and the resulting solution was stirred at 25 °C for 12 h. The solution was diluted with ether and was extracted three times with water and was dried. Removal of the solvent gave 4.94 g of crude **22**. Purification of a 1.70-g portion by flash chromatography on silica gel (95:5 hexane/EtOAc) gave 0.901 g (53% from the ketone) of **22** as an inseparable 3:2 mixture of isomers containing 5–10% of the isomer resulting from γ addition in the Reformatsky reaction: IR (neat) 2960, 2881, 1740, 1645, 1444, 1386, 1318, 1220, 1140, 1113, 1075, 1022, 983, 910 cm^{-1}.

The data for the major isomer were obtained from the mixture: ^{1}H NMR 6.59 (dd, 1, J = 11.0, 17.4), 5.13 (br d, 1, J = 11.0), 5.08–5.22 (m, 1), 5.07 (br d, 1, J = 17.4), 3.81 (s, 3), 2.22 (m, 2), 2.14 (m, 2), 1.83 (s, 3), 1.69 (s, 3), 1.61 (s, 3); ^{13}C NMR 170.0, 141.0, 132.6, 132.3, 130.2, 123.2, 114.9, 51.6, 33.8, 26.6, 25.6, 21.1, 17.6.

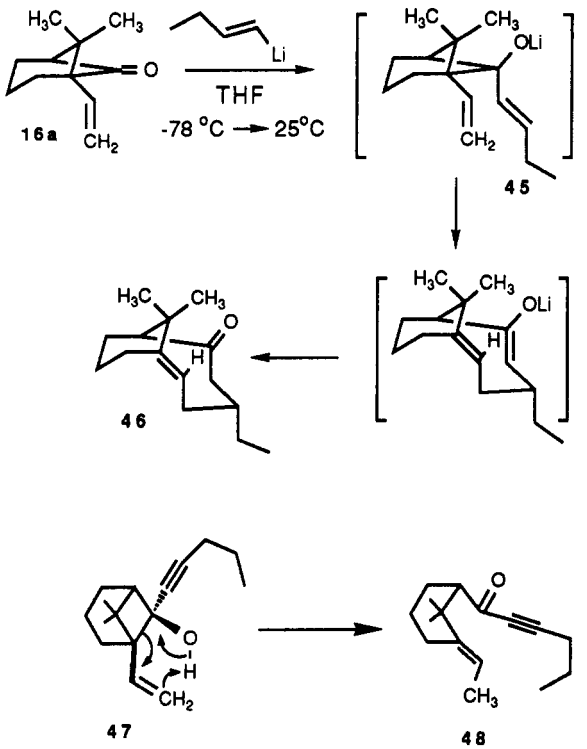
The data for the minor isomer were obtained from the mixture: ^{1}H NMR 6.57 (dd, 1, J = 11.0, 17.4), 5.08–5.22 (m, 1), 5.16 (br d, 1, J = 11.0), 5.08 (br d, 1, 17.4), 3.78 (s, 3), 2.22 (m, 2), 2.14 (m, 2), 1.86 (s, 3), 1.69 (s, 3), 1.61 (s, 3); ^{13}C NMR 170.0, 141.0, 132.6, 132.3, 130.2, 123.4, 115.2, 51.6, 37.4, 26.7, 26.3, 21.1, 17.6.

(*E*)- and (*Z*)-3,7-Dimethyl-2-ethenyl-2,6-octadienoic Acid (23a) and (*E*)-2-Ethylidene-3-methylene-7-methyloct-6-enoic Acid (23b). Ester mixture **22** (0.842 g, 4.04 mmol) was added to a mixture of anhydrous lithium hydroxide[20] (0.968 g, 40.4 mmol) in DME (50 mL) and water (20 mL), and the mixture was stirred at 25 °C for 24 h. This mixture was then diluted with water (25 mL) and was extracted three times with ether. The solvent was removed from the organic layer to give **22** free of the isomer resulting from γ addition in the Reformatsky reaction.

Ester **22** was then added to a mixture of lithium hydroxide, DME, and water as described above, and the reaction mixture was heated at reflux for 96 h and was worked up to give 0.661 g of crude material. Purification of a 0.641-g portion by flash chromatography on silica gel (60:40:0.2 hexane/EtOAc/AcOH) gave 0.565 g (74%) of a 3:5:2 mixture of the two stereosiomers of **23a** and **23b**, respectively: IR (neat) 2963, 2920, 1692, 1628, 1410, 1375, 1272, 1235, 978, 905 cm^{-1}; ^{1}H NMR minor stereoisomer of **23a** 6.56 (dd, 1, J = 17.3, 11.0), 5.27 (d, 1, J = 17.3), 5.20 (d, 1, J = 11.0), 5.12 (m, 1), 2.19–2.33 (m, 2), 2.04–2.18 (m, 2), 1.89 (s, 3), 1.69 (br s, 3), 1.61 (br s, 3); ^{1}H NMR major stereoisomer of **23a** 6.58 (dd, 1, J = 17.3, 11.0), 5.27 (d, 1, J = 17.3), 5.20 (d, 1, J = 11.0), 5.12 (m, 1), 2.19–2.33 (m, 2), 2.04–2.18 (m, 2), 1.97 (s, 3), 1.69 (br s, 3), 1.61 (br s, 3); ^{1}H NMR **23b** 7.11 (q, 1, J = 7.1), 5.12 (m, 2), 4.85 (d, 1, J = 2.0), 2.19–2.33 (m, 2), 2.04–2.18 (m, 2), 1.86 (d, 3, J = 7.1), 1.69 (br s, 3), 1.61 (br s, 3). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.26; H, 9.37.

7,7-Dimethyl-1-ethenyl-2-methylenebicyclo[3.1.1]heptan-6-one (5). The acid mixture **23** (0.373 g, 1.92 mmol) was converted to acid chloride **24** by treatment with oxalyl chloride (1.21 g, 9.60 mmol) and NaH (0.230 g of a 60% dispersion washed twice with hexanes, 5.76 mmol) in benzene as previously described. Acid chloride **24** was dissolved in benzene and the resulting solution was added dropwise to a solution of Et_3N (1.55 g, 15.4 mmol) in benzene at reflux as previously described. Workup followed by flash chromatography on methanol-deactivated silica gel (96:4 pentane/ether) gave 0.117 g (29%) of pure **5**: ^{1}H NMR 5.77 (dd, 1, J = 17.9, 11.2), 5.45 (dd, 1, J = 17.9, 2.0), 5.30 (dd, 1, J = 11.2, 2.0), 4.88 (dddd, 1, J = 1, 1, 1, 1), 4.78 (br d, 1, J = 2.3), 2.68 (dd, 1, H_5, J = 4.9, 2.1), 2.44 (br dddd, 1, J = 16, 8, 1.6, 1), 2.33 (dddd, 1, J = 16.5, 9.3, 2.5, 2.5), 2.04–2.24 (m, 2), 1.09 (s, 3), 1.07 (s, 3); ^{13}C NMR 210.1 (C=O), 150.7 (C=, C_2), 130.4 (HC=), 118.0

Scheme VIII



(H_2C=), 109.5 (exo H_2C=), 77.1 (C, C_1), 62.5 (CH, C_5), 35.3 (C, C_7), 26.7 (CH_2), 25.7 (CH_2), 24.7 (CH_3), 17.8 (CH_3); IR (neat) 2922, 1776, 1634, 1451, 1318, 921, 884 cm^{-1}; exact mass calcd for $C_{12}H_{16}O$ 176.1202, found 176.1200.

(*E*)-11,11-Dimethyl-8-methylenebicyclo[5.3.1]undec-6-en-2-one (27). Ketone **5** (47.9 mg, 0.272 mmol) in 1 mL of THF was added at −78 °C via syringe to a stirred solution of vinyllithium (0.24 mL of a 1.7 M solution in THF, 0.408 mmol) in THF at −78 °C as previously described. After addition, the solution was stirred at −78 °C for 1 h. The reaction was quenched at −78 °C by careful dropwise addition of water. The solution was allowed to warm to 25 °C and was worked up to give 65.4 mg of crude product. Purification of a 56.3-mg portion by flash chromatography on methanol-deactivated silica gel (96:4 hexane/EtOAc) gave 9.1 mg (19%) of pure **27**: mp 74–75 °C; ^{1}H NMR 5.12 (dd, 1, H_6, J = 12.1, 4.2), 4.96 (br ddd, 1, J = 2.2, 2, 2), 4.85 (br ddd, 1, J = 2.2, 2, 2), 2.81–3.07 (m, 2), 2.53 (dddd, 1, J = 12.1, 12.3, 12, 4.1), 2.29–2.44 (m, 2), 1.67–2.20 (m, 6), 1.20 (s, 3), 1.12 (s, 3); ^{13}C NMR 215.6 (C=O), 151.6 (C=), 145.6 (C=), 123.7 (HC=), 112.7 (H_2C=), 66.2 (CH, C_1), 45.3 (C, C_{11}), 39.0 (CH_2), 32.3 (CH_2), 30.7 (CH_2), 27.8 (CH_2), 25.0 (CH_3), 23.0 (CH_3), 19.3 (CH_2); IR ($CDCl_3$) 2936, 2777, 1685, 1467, 1450, 1387, 1371, 1324, 1290, 1210, 1169, 1114 cm^{-1}; UV (cyclohexane) λ_{max} (ϵ) 212 (1982), 244 (2185). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.97; H, 9.70.

1-(2-Methyl-1-cyclohexen-1-yl)-6-ethenyl-7-methyl-6-octen-1-one (34). 1-Iodo-2-methylcyclohexene[15] (55.8 mg, 0.340 mmol) was dissolved in THF (3 mL) and was treated with *tert*-butyllithium (0.60 mL of a 1.7 M solution in pentane, 1.02 mmol) at −78 °C.[16] The resulting yellow solution was stirred at −78 °C for 30 min. Ketone **16a** (55.8 mg, 0.340 mmol) was added at −78 °C as previously described, and the solution was stirred at −78 °C for 1 h, allowed to warm to 25 °C, and stirred for 1 h. Workup gave 93.7 mg of crude product. Purification of an 84.6-mg portion of the crude material by flash chromatography on silica gel (95:5 hexane/EtOAc) gave 34.2 mg (43%) of pure **34**: ^{1}H NMR 6.72 (dd, 1, J = 17.4, 11.0), 5.08 (d, 1, J = 17.4), 4.96 (d, 1, J = 11.0), 2.51 (dd, 2, J = 7.4, 7.1), 2.25 (br dd, 2, J = 8.1, 7), 2.21 (m, 1), 2.06 (m, 1), 1.72–1.91 (m, 2), 1.80 (s, 3), 1.78 (s, 3), 1.54–1.71 (m, 4), 1.61 (br s, 3), 1.22–1.46 (m, 4); ^{13}C NMR 207.5, 138.7, 134.6, 133.5, 131.6, 131.4, 110.7, 41.5, 32.6, 31.6, 28.7, 27.7, 26.6, 24.4, 22.6, 22.3, 20.2, 14.1; IR (neat) 2934, 2864, 1686, 1636, 1450, 1378, 914, 733 cm^{-1}.

1-Ethenyl-7,7-dimethyl-6-(2-methyl-1-cyclohexen-1-yl)bicyclo[3.1.1]heptan-6-ol (31b). 1-Iodo-2-methylcyclohexene[15] (0.180 g, 0.810 mmol) was treated with *tert*-butyllithium (0.95 mL of a 1.7 M solution in pentane, 1.68 mmol) at −78 °C in THF as previously described. Ketone **16a** (0.089 g, 0.54 mmol) was added at −78 °C via syringe over 4 min as described above. The solution was stirred at −78 °C for 1.5 h and was then quenched by slow, dropwise addition of AcOH (0.130 g, 2.16 mmol) at −78 °C. The solution was allowed to warm to 25 °C, and saturated aqueous bicarbonate solution was added. Workup gave 0.150 g of crude **31b**. Purification of a 0.138-g portion by flash chromatography on silica gel (97:3 hexane/EtOAc) gave 83.5 mg (70%) of pure **31b**: ^{1}H NMR 6.40 (dd, 1, J = 18.0, 11.2), 5.02 (dd, 1, J = 11.2, 2.1), 4.88 (dd, 1, J = 18.0, 2.1), 2.28 (dd, 1, J = 3.1, 2.9), 1.77–2.09 (m, 6), 1.08–1.77 (m, 8), 1.74 (br s, 3), 1.44 (s, 3), 0.82 (s, 3); ^{13}C NMR 139.0 (HC=), 137.0 (C=), 128.6 (C=), 112.4 (H_2C=), 84.0 (C—OH), 52.5 (CH), 52.3 (C), 41.8 (C), 32.9 (CH_2), 28.1 (CH_2), 26.4 (CH_2), 26.4 (CH_3), 24.6 (CH_2), 23.8 (CH_2), 23.1 (CH_2), 21.8 (CH_3), 20.1 (CH_3), 15.2 (CH_3); IR (neat) 3470, 2930, 2865, 1630, 1450, 1335, 1319, 1215, 1060, 1010, 1000, 910 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.89; H, 10.78.

(*E*)-3-Ethylidene-2,2-dimethylcyclohexyl 2-Methyl-1-cyclohexenyl Ketone (39). Alcohol **31b** (14.0 mg, 0.054 mmol) was dissolved in 2 mL of C_6D_6 containing a drop of pyridine. The solution was sealed in an NMR tube and was heated in an oil bath at 85 °C for 37 h.[6g] The formation of product was monitored by ^{1}H NMR. When a spectrum was taken, the sample was removed from the oil bath and allowed to cool to 25 °C, and the spectra was recorded at probe temperature. After the reaction was completed, the solvent was removed under vacuo to give crude **39**. Flash chromatography on silica gel (97:3 hexane/EtOAc) gave 10.5 mg (75%) of pure **39**: ^{1}H NMR 5.21 (q, 1, J = 7.4), 2.85 (dd, 1, J = 8.5, 4.6), 2.13–2.36 (m, 4), 2.06 (m, 3), 1.52–1.81 (m, 7), 1.76 (br d, 3, J = 7.4), 1.59 (s, 3), 1.29 (s, 6); ^{13}C NMR 210.0 (C=O), 144.3 (C=), 138.8 (C=), 134.7 (C=), 116.8 (HC=), 56.3 (CH), 41.0 (C), 35.9 (CH_2), 32.7 (CH_2), 28.9 (CH_3), 27.0 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 25.0 (CH_3), 22.5 (CH_2), 22.3 (CH_2), 21.4 (CH_3), 14.9 (CH_3); IR (neat) 2930, 2860, 1680, 1446 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.09; H, 10.86.

(*E*)-7,7-Dimethyl-4-ethylbicyclo[5.3.1]undec-6-en-2-one (46). *tert*-Butyllithium (0.32 mL of a 1.7 M solution in pentane, 0.552 mmol) was added dropwise to a solution of (*E*)-1-bromobutene (37.0 mg, 0.276 mmol) in 3 mL of THF under nitrogen at −78 °C.[16] The resulting yellow solution was stirred at −78 °C for 30 min. A solution of ketone **16a** (30.2 mg, 0.184 mmol) in 1 mL of THF was then added via syringe at −78 °C as previously described. The solution was stirred at −78 °C for 30 min, allowed to warm to 25 °C over 2 h, and stirred at 25 °C for 1 h. The reaction was quenched and worked up to give 37.2 mg of crude product. Purification of a 34.0-mg portion of the crude material by flash chromatography on silica gel (95:5 hexane/EtOAc) gave 11.2 mg (30%) of pure **46** as a viscous oil: ^{1}H NMR 5.08 (br ddd, 1, H_6, J = 11.5, 3.7, 1.5), 2.67 (dd, 1, J = 14.4, 9.8, H_8), 2.34–2.49 (m, 2), 1.73–2.35 (m, 9), 1.40 (dq, 2, J = 7, 7.3), 1.25 (s, 3), 1.19 (s, 3), 0.946 (t, 3, J = 7.3); ^{13}C NMR 214.9 (C=O), 146.5 (C=, C_7), 121.0 (HC=), 66.1 (CH, C_1), 46.8 (CH, C_4), 46.2 (CH_2), 45.3 (C, C_{11}), 34.8 (CH_2), 29.5 (CH_2), 24.4 (CH_2), 23.8 (CH_3), 23.4 (CH_3), 20.9 (CH_2), 20.8 (CH_2), 11.7 (CH_3); IR (neat) 2965, 2931, 1684, 1465, 1390, 1040, 880 cm^{-1}.

Acknowledgment. Support by the National Institutes of Health is gratefully acknowledged.

Registry No. (±)-**5**, 129966-86-5; **8a**, 63588-94-3; **8b**, 112683-29-1; **9a**, 129966-87-6; **9b**, 129966-88-7; (±)-**10a**, 129966-89-8; **11a**, 129966-90-1; **11b**, 129966-91-2; (±)-**12a**, 129966-92-3; **13a**, 129966-93-4; **13b**, 129966-94-5; (±)-**14a**, 129966-95-6; **15a**, 129966-96-7; **15b**, 129966-97-8; (±)-**16a**, 129966-98-9; (±)-**16b**, 129985-12-2; (±)-**17b**, 129966-99-0; (±)-**20a**, 129967-00-6; (±)-**20b**, 129967-01-7; (±)-**21** (isomer 1), 129967-02-8; (±)-**21** (isomer 2), 129967-22-2; (*E*)-**22**, 129967-04-0; (*Z*)-**22**, 129967-03-9; (*E*)-**23a**, 129967-23-3; (*Z*)-**23a**, 129967-05-1; **23b**, 129967-06-2; (*E*)-**24a**, 129967-24-4; (*Z*)-**24a**, 129967-07-3; **24b**, 129967-25-5; (±)-**27**, 129967-08-4; (±)-**31b**, 129967-09-5; **34**, 129967-10-8; (±)-**35**, 129967-11-9; (±)-**36**, 129967-12-0; (±)-**37**, 129967-13-1; (±)-**38**, 129967-14-2; (±)-**39**, 129967-15-3; (±)-**40**, 129967-16-4; (±)-**41**, 129967-17-5; (±)-**42**, 129967-18-6; (±)-**43**, 129967-19-7; (±)-**44**,

129967-20-0; (±)-46, 129967-21-1; methyl crotonate, 623-43-8; 6-methylhept-5-en-2-one, 110-93-0; methyl 4-bromocrotonate, 6000-00-6; 1-iodo-2-methylcyclohexene, 40648-08-6; (*E*)-1-bromo-1-butene, 32620-08-9; 1-bromo-2-methyl-1-propene, 3017-69-4; (*Z*)-1-bromo-1-propene, 590-13-6; 2-bromo-1-propene, 557-93-7; 1-iodocyclohexene, 17497-53-9.

Supplementary Material Available: Experimental details for the preparation of **35–38** and **40–44** (4 pages). Ordering information is given on any current masthead page.

Manganese(III)-Based Asymmetric Oxidative Free-Radical Cyclization of Unsaturated β-Keto Sulfoxides

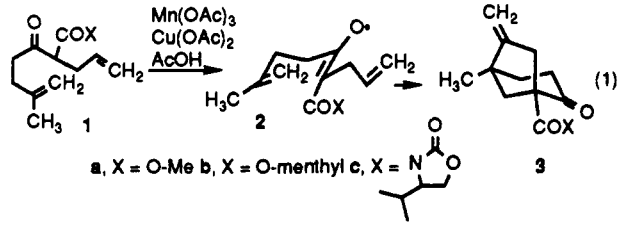
Barry B. Snider,* Barbara Yu-Fong Wan, Brad O. Buckman, and Bruce M. Foxman

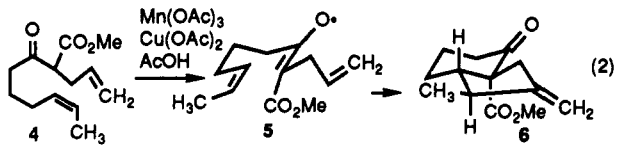
Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254-9110

Received June 5, 1990

β-Keto sulfoxides and β-keto sulfones can be used as substrates for Mn(III)- and Cu(II)-based oxidative free-radical cyclizations. The sulfoxide chiral center completely controls the stereochemistry of the cyclization. Oxidative cyclization of racemic sulfoxide **8** affords **13** as a single diastereomer. Oxidative cyclization of enantiomerically pure sulfoxide **20** gives **21** as a single enantiomer. The chiral auxiliary can be removed by oxidation with potassium peroxomonosulfate to give the sulfone followed by reduction with sodium amalgam to give bicyclo[3.2.1]octanone **23**. Oxidative cyclization of **26** gives indanone **29**, which spontaneously loses toluenesulfenic acid to give indenone **30**.

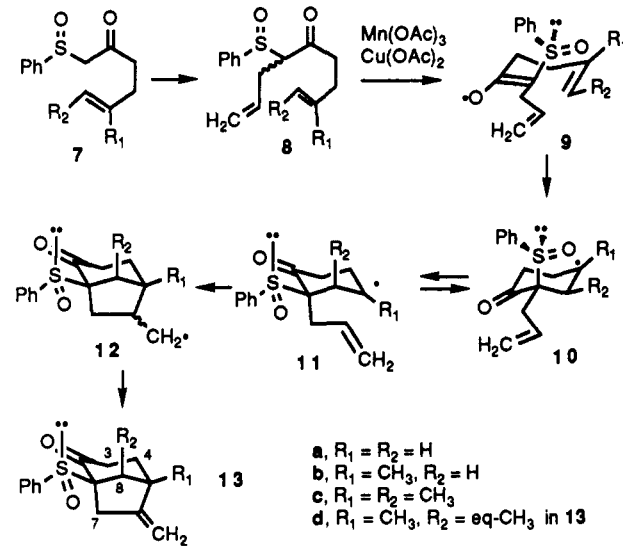
We have recently developed Mn(III)-based oxidative free-radical tandem cyclizations into a general route for the preparation of bicyclo[3.2.1]octan-2-ones **3a** (eq 1) and indenones **6** (eq 2).[1] Since these cyclizations proceed





through achiral radicals **2a** and **5** to produce chiral products **3a** and **6**, we have examined modifications using chiral auxiliaries that would permit these cyclizations to be carried out with asymmetric induction. Initial studies using **1b**, X = *O*-menthyl, were discouraging, affording ≈55:45 mixtures of diastereomers. We next turned our attention to Evans' chiral oxazolidinone, which gives much higher asymmetric induction than chiral esters.[2] Unfortunately, **1c** did not undergo oxidative cyclization on treatment with Mn(III) and Cu(II) in acetic acid. We therefore turned our attention to the oxidative cyclization of β-keto sulfoxides rather than β-keto esters. Sulfoxides have been used successfully in asymmetric carbon–carbon

Scheme I



bond-forming reactions.[3] The proximity of the sulfur chiral center to the radical should lead to a high degree of asymmetric induction if the oxidative cyclization is successful.

Results and Discussion

The requisite β-keto sulfoxides can be easily prepared by standard procedures. Our initial studies were carried out with racemic sulfoxides since the extent of asymmetric induction in the cyclization could be easily determined as

(1) (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (b) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759 and references cited therein. (c) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427 and references cited therein.

(2) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(3) Posner, G. H. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C., Eds.; John Wiley & Sons: Chichester, 1988; pp 823–849. Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, pp 225–241. Solladié, G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, pp 157–199. Barbachyn, M. R., Johnson, C. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 4, pp 227–261.

0022-3263/91/1956-0328$02.50/0